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ACTH AND CORTISONE IN THE TREATMENT OF ULCERATIVE COLITIS*

An Evaluation of their Prolonged Administration

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SAN FRANCISCO

THE extensive employment of ACTH and cortisone in the treatment of idiopathic ulcerative colitis has now been fully reported.[1-6] The general experience has been that these hormones are initially and often strikingly effective in suppressing the secondary symptoms and toxic effects of this disease. Most observers, however, have also noted that cessation of such therapy is followed by a disappointing recurrence of symptoms. Apparently, short-term therapy does not reverse the underlying pathologic process.

The short-term use (three months or less) of ACTH in the medical management of 33 patients with ulcerative colitis has previously been reported by Elliott, Kiefer and Hurxthal.[7] Treatment resulted in symptomatic benefit in 21 cases; in a follow-up study two years later, however, signs of apparent remission were found in only 12 of the patients.[8] These results are no better than the response of 50 to 60 per cent reported with other types of medical treatment.[9-11] On the other hand therapy with ACTH and cortisone returns severely ill patients to apparent good health with unparalleled rapidity. Such a prompt reversal, even if transitory, is difficult to disregard in any condition characterized by acute protracted exacerbation, prolonged disability, stubborn resistance to treatment and disastrous complications.

MATERIALS AND METHODS

Thirteen cases of ulcerative colitis were selected for study. The patients had failed to respond to the usual medical measures, including hospital care, diet, antibiotics, transfusion and, in several cases, psychotherapy. To allow proper comparison the cases chosen ranged from acute fulminant colitis of recent origin to long-standing, chronically active disease. The range of anatomic involvement varied from segmental inflammation of the lower sigmoid colon to extensive ulceration of the entire large bowel and distal ileum.

Since it was our purpose to evaluate the effects of the agents on the pathologic process the criteria of response were confined to signs of objective clinical improvement, as determined by sigmoidoscopic and radiologic examinations. Although impressive subjective improvement was reported by our patients, we do not believe that a ravenous appetite, euphoria and the now familiar metabolic effects of corticotherapy constitute basic clinical guides. The usual laboratory criteria of adrenocortical response were employed. Determinations of urinary steroid levels and circulating eosinophil counts were not sufficiently reliable to serve as guides to dosage. These tests, however, were useful in detecting resistance to ACTH.

All patients were hospitalized during the initial stages of treatment with ACTH and cortisone, and all were subsequently followed in the Gastrointestinal Clinic of the University of California Hospital. No patient was treated for less than five months, and several were treated almost continuously for two years.

Several preparations of ACTH, administered by various routes, were employed. A few patients were treated with cortisone alone, and several with ACTH followed by cortisone as maintenance therapy. In all cases the dose was determined by the therapeutic response.

REPRESENTATIVE CASE REPORTS

CASE 1. D. W. (U185178), a 28-year-old housewife, was first seen at the University of California Hospital on January 5, 1951, with a complaint of bloody diarrhea of 3 years' duration. She was followed in the Outpatient Department for 8 months, during which increased rest and use of demulcents, folic acid, testosterone and antispasmodics had no significant effect.

Administration of lyophilized ACTH (Armour), 15 mg. every 6 hours by intramuscular injection, was instituted on August 18 (Fig. 1). The patient's appetite promptly increased; the diarrhea decreased to passage of 1 semiformed stool a day. She was discharged 1 week later. ACTH was gradually decreased over the next 6 weeks to 30 mg. a day in divided doses. Coincident with the gradual withdrawal of ACTH, mild diarrhea, with occasional passage of blood-streaked stools, returned.

On October 1 long-acting ACTH (Armour), 40 units a day, was substituted. A tremendous return of appetite and

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energy and improvement of spirits occurred. The cramps ceased rapidly, and the stools decreased to 1 or 2 a day. During the next 3 months on this dosage schedule bowel and systemic symptoms slowly returned. Increasing the dose to 80 units a day had no effect. It was apparent that resistance to ACTH had developed.

The patient was readmitted to the hospital on January 24, 1952. She was then given 40 units a day of a more purified

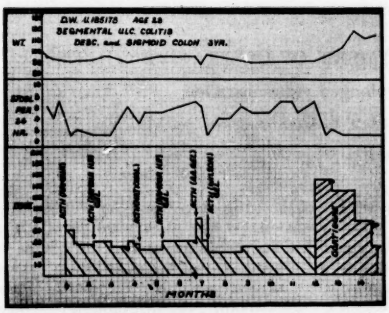

FIGURE 1. *Effect of ACTH on the Symptoms in Case 1.*

preparation of ACTH (ACTHAR H.P.). Again, the response was prompt; all symptoms rapidly subsided, and secondary metabolic effects were far more intense than those previously observed. The laboratory criteria of adrenocortical stimulation paralleled this therapeutic response (Fig. 2). The patient was discharged 4 days later on a regimen of ACTH (Wilson), 20 units daily, with continued evidence of adrenocortical stimulation. The next 3 months were again characterized by a slow return of symptoms; however, repeated sigmoidoscopic examination revealed a significant lessening of the inflammation. With reduction in the dose of ACTH to 20 units daily, diarrhea increased to the passage each day of 2 to 4 semiliquid mucoid stools, occasionally streaked with blood.

Administration of cortisone, 50 mg. 3 times daily by mouth, was started on June 2. It resulted in a response

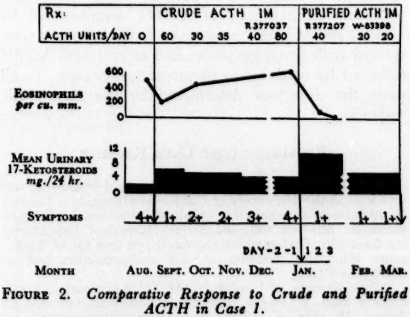

FIGURE 2. *Comparative Response to Crude and Purified ACTH in Case 1.*

equally as prompt and as dramatic as that previously noted with ACTH. Diarrhea decreased to the passage of 1 or 2 formed, nonbloody, apparently normal stools daily. A 7-kg. increase in weight occurred. Cortisone was gradually reduced and was finally discontinued on October 20. The patient was clinically well and remained so, living a completely normal life. Four months later, sigmoidoscopic examination showed a narrowed, rigid sigmoid colon with pseudopolyps, but there was no gross evidence of inflammation. Six months later the patient was continuing to take cortisone by mouth and was leading a normal life.

This case of segmental ulcerative colitis with involvement of only the descending and sigmoid colon was characterized by fairly severe secondary systemic reactions. Although no real remissions had occurred before hormonal therapy the limited pathologic process and toxic symptoms suggested medical rather than surgical measures as the initial treatment of choice. The escape of the colitis from control, with the development of resistance or refractoriness to ACTH and the subsequent response to a more purified preparation of ACTH, is commented on below in the discussion.

CASE 8. H. V. (U193624), a 34-year-old housewife, was admitted to the University of California Hospital on August 15, 1951, complaining of bloody diarrhea of 2 months' duration. Barium-enema and sigmoidoscopic examinations revealed acute ulcerative colitis of recent origin involving the entire colon.

Lyophilized ACTH (Armour), 15 mg. daily, intravenously, was started on August 23. After 1 week long-acting ACTH,

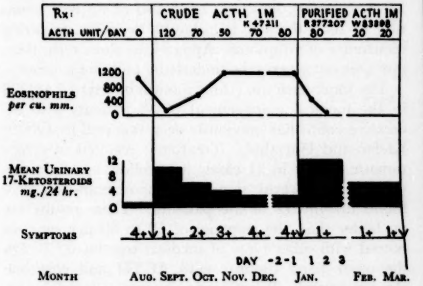

FIGURE 3. *Therapeutic Response in Case 8.*

120 units daily, was substituted. Pronounced metabolic effects of adrenocortical stimulation were noted. Sigmoidoscopic study showed no lessened edema and exudation. Barium-enema examination disclosed changes toward normal; the caliber of the lumen of the colon had increased, and the mucosal pattern was somewhat less distorted. The patient was discharged on October 4, showing considerable improvement in appetite and strength, a 4-kg. gain in weight and complete disappearance of fever and other signs of general toxicity.

During the next 2 months the discharge dose of 80 units of ACTH (ACTHAR gel) daily was gradually reduced to 50 units. At this point another ACTH preparation (National ACTH) was substituted. The improvement was maintained. By December, however, diarrhea and cramps had increased gradually, and the secondary metabolic characteristics had lessened. Coincident with this, the number of circulating eosinophils had risen, and the urinary excretion of 17-ketosteroids had decreased (Fig. 3). It was apparent that, as in Case 1, resistance to ACTH had developed.

The patient was readmitted to the hospital on December 28. Administration of a more purified preparation of ACTH (ACTHAR H. P.), was started early in January, 1952. Again an immediate, favorable response occurred. The stools became formed; cramps, tenesmus and fever rapidly disappeared, and pronounced facial fullness, acne and euphoria returned. The appetite became ravenous, and 4.5 kg. of weight was gained abruptly. As in Case 1 the laboratory

criteria of adrenocortical stimulation paralleled the therapeutic response (Fig. 3).

The patient was discharged on January 23. During the next few months ACTH was gradually reduced to 10 units a day; it was finally discontinued on April 21. She resumed the active life of a housewife. A further gain of 8 kg. in weight occurred. The stools were entirely normal. Sigmoidoscopic examination showed appreciable scarring and narrowing of the colon, but there was no evidence of ulceration or any degree of inflammation.

The patient has been seen periodically since that time. Barium-enema study in November, 1952, demonstrated return of segmentation and haustration, changes toward normal.

This case is representative of acute ulcerative colitis of short duration, with severe systemic symptoms and extensive inflammatory involvement of the colon. In our experience cases of this type usually respond well to ACTH. In this particular patient the acute manifestations were suppressed rapidly. The colitis is now in complete remission. It cannot be claimed that ACTH "cured" the disease, but it certainly shortened the acute episode. As in Case 1 control of the disease depended on adequate adrenocortical stimulation. This was obtained only by the administration of highly purified ACTH preparations.

Case 6. F. C. (U189651), a 60-year-old architect, was admitted to the hospital on February 29, 1952, complaining of severe bloody diarrhea of 4 months' duration. There had been an 11.5-kg. weight loss and intermittent fever.

The initial therapeutic program, consisting of a high-protein, low-residue diet, vitamins, demulcents and antispasmodics, resulted in no change. ACTH (Wilson soluble), 20 units every 6 hours, intramuscularly, which was begun on March 5 and continued for 4 weeks, had a slight clinical response. The urinary excretion of 17-ketosteroids was low. Accordingly, different preparations of ACTH, Upjohn cortisone, 25 units every 6 hours, intramuscularly, and National ACTH, 40 units every 12 hours, were used during the next 10 days, again without significant clinical or metabolic response. On April 16 ACTHAR gel, 40 units every 24 hours, was substituted. Slow but progressive clinical improvement occurred, and for the first time there was laboratory evidence of adrenocortical stimulation.

On discharge to the Outpatient Department on May 20 the patient continued to take 40 units of ACTH daily (Wilson ACTH gel), with continued laboratory evidence of adrenocortical stimulation. He averaged 4 or 5 semiformed stools a day, cramps had disappeared, appetite had increased, and a 10-kg. weight gain had occurred since admission to the hospital. Barium-enema study again showed the entire colon to be involved; the mucosal pattern was disturbed, and ulceration was apparent, particularly in the descending colon. Definite improvement, however, was noted in the ascending and transverse colon, as compared to the status in previous films.

Because the patient suffered from increasing nervous irritability and insomnia, ACTH was discontinued on June 2, and cortisone, 50 mg. 4 times a day by mouth, was substituted. He failed to respond; diarrhea returned, and cortisone, 200 mg., 3 times a week, intramuscularly, was added to the oral dose of cortisone. Two weeks later he reported gradual but definite improvement and a rapid gain of 4.5 kg. in weight. Cortisone was discontinued on July 14 (approximately 6 weeks later), and a clinical trial of hydrocortisone acetate, 50 mg. 4 times a day by the oral route, was instituted. No benefit greater than that obtained with cortisone was noted, and cortisone, 50 mg. 4 times a day by mouth, was substituted. Three weeks later he was feeling well; rectal discharge, occasionally urgent, averaged 2 to 4 semiformed stools per 24 hours. His face was full, but otherwise surprisingly little secondary hormonal effect was apparent. Barium-enema study in August demonstrated no progressive or regressive changes. Sigmoidoscopic examination at that time, and also in October, revealed an edematous, friable mucosal surface that bled easily; there was no evidence of ulceration.

During the next 6 months cortisone was administered continuously (200 mg. daily in 4 divided doses). The patient felt well and returned to his former occupation; rectal discharge averaged 2 or 3 formed stools daily. However, barium-enema examination in March, 1953, showed, in addition to the abnormalities described above, numerous small, radiolucent filling defects throughout the lower descending colon. Sigmoidoscopic examination confirmed the presence of many pseudopolyps in the rectosigmoid. The entire mucosa was red, boggy and friable. In spite of this evidence of an active and progressive process, the patient continued to be relatively free of symptoms.

In this case the pathologic process was acute and extensive. The symptomatic and subjective response was striking. The underlying process was apparently unaffected, as manifested by the persistence of inflammation in the mucosa of the rectosigmoid. Moreover, pseudopolypoid degeneration occurred during the period of continuous therapy. The dissociation between clinical symptoms and pathologic changes was noteworthy. Although this phenomenon was occasionally observed before the advent of ACTH and cortisone, it is worth emphasizing that ACTH and cortisone, even when effective, may suppress the clinical and laboratory manifestations of the disease without reversing the pathologic process.

Again, clinical response to ACTH depended on adequate adrenocortical stimulation; several preparations of ACTH failed to have this effect.

Case 9. E. H. (U196749), a 26-year-old housewife, was admitted to the hospital in November, 1951, because of recurrent diarrhea of 4 years' duration. Barium-enema examination showed shortening and narrowing of the entire colon. X-ray studies of the small bowel demonstrated irritability, pipestemming, and complete distortion of the mucosal pattern in the lower ileum. The diagnosis was "recurrent enterocolitis, now in exacerbation, with moderate to severe secondary 'toxic' systemic symptoms."

The patient failed to respond to general supportive hospital care. Consequently, cortisone (Merck), 100 mg. intramuscularly, was administered twice daily for 9 days, beginning on December 1 (Fig. 4). No effect was noted.

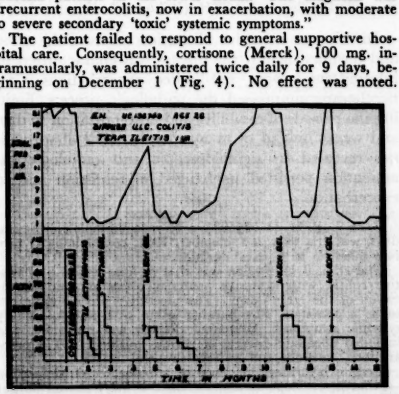

Figure 4. *Response to Cortisone and ACTH in Case 9.*

ACTH (ACTHAR, lyophilized), 25 units daily by slow intravenous infusion, was then substituted. Within 48 hours there was a dramatic response. Rectal discharge decreased to 1 or 2 semiformed stools a day, abdominal cramps disappeared completely, appetite increased considerably, and

the patient became euphoric. ACTH was gradually decreased during the next 2 weeks; she was then given long-acting ACTH (ACTHAR gel), 30 units every 12 hours, intramuscularly. After 1 month of this treatment the food intake had increased to 4300 calories a day; stools averaged 1 or 2 a day, and no cramps or passage of blood was noted. Euphoria and restlessness increased rapidly and merged into a definitely psychotic picture. Suicidal impulses and ideas of self-depreciation were expressed; fear of insanity and increasing restlessness became prominent. ACTH was necessarily discontinued. Psychotherapeutic procedures were instituted, and she responded rapidly. (The psychiatric features of this case will be discussed in a separate report.) Within the next 4 weeks, however, diarrhea and abdominal cramps gradually returned, and appetite decreased. On February 12, 1952, ACTH (Wilson ACTH gel), 20 units daily intramuscularly, was administered; a week later the dose was increased to 30 units daily. The patient again improved, and after 1 month the dose was reduced to 15 units daily. ACTH was discontinued after 3 months, when she had few or no subjective symptoms and had gained 5 pounds in weight. No apparent adverse psychologic effects were noted during this 2d administration period; psychiatric treatment was closely integrated with medical management throughout this time.

During the next 3 months diarrhea, cramps and weakness returned, and the patient lost weight. Administration of ACTH (Wilson ACTH gel), 40 units daily injected intramuscularly, was started again in July. Once more a satisfactory response occurred, with rapid cessation of diarrhea and gain in weight. The patient found it difficult to adjust herself to feeling so well so quickly. ACTH was discontinued 1 month later because of increasing mental depression, confusion and tension; within 2 weeks severe bowel symptoms returned. This exacerbation, which was more fulminating than previous relapses, was marked by agonizing cramps, rapid loss of weight and passage of countless bloody, liquid stools.

Administration of ACTH (Wilson gel) was started again on September 20, and diarrhea and cramps were suppressed and subjective improvement occurred.

Symptomatic improvement was maintained until the latter part of December. Then, coincident with environmental stresses and respiratory infections, recurrence of abdominal cramps, rectal urgency and increasing liquid, bloody diarrhea necessitated readmission to the hospital on January 22, 1953. This recurrence seemed to be severe but responded promptly to moderate doses of ACTH (Wilson gel, 40 units daily).

In this case extensive ulceration involved the colon and terminal ileum; the disease was characterized by intermittent, severe, self-limited exacerbations. Corticotherapy suppressed the pathologic process, limiting the periods of disability and hospitalization to days and weeks instead of many months. The abnormalities revealed by sigmoidoscopic and radiologic examination persisted unchanged in remission and in exacerbation.

Case 7. P. M. (U194502), a 25-year-old male college student, was first seen in September, 1951, complaining of profuse diarrhea of 4 years' duration.

The clinical impression was that of long-standing ulcerative colitis, with extensive anatomic alteration and scarification of the large bowel. The ulcerative process appeared to be a persistent, slow-burning affair, with mild secondary systemic symptoms. Hormonal therapy was instituted, and included adequate dosages of various purified ACTH preparations, cortisone and hydrocortisone.

Despite laboratory evidence of adrenocortical stimulation — that is, eosinopenia and increased urinary steroid output (Fig. 5) — none of the other familiar secondary metabolic effects were obtained with any of the preparations used. The clinical picture was also unaltered. It was believed that adequate doses had been used over a sufficient length of time. Subsequent treatment with sulfonamides, chlortetracycline and an allergic type of elimination diet for 5 months was ineffective.

The disease in this case was characterized by extensive anatomic changes, the result of past acute phases of the disease. When the patient came under our care, the symptoms were due to extensive cicatrization of the bowel, coupled with low-grade inflammation. It

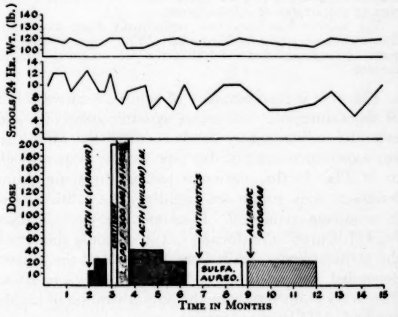

Figure 5. *Failure of Various Types of Therapy in Case 5.*

seems likely that patients with this form of the disease will not respond significantly to ACTH or cortisone. These agents have an anti-inflammatory effect; they cannot restore function to a rigid and stenotic colon.

Case 11. K. R. (U161195), a 26-year-old entertainer, underwent an ileostomy in March, 1950, for severe and intractable ulcerative colitis of 2 years' duration. She enjoyed good health until August, 1951, when episodes of malaise, fever, articular pain, sanguineous rectal discharge and profuse ileal drainage occurred. Studies revealed active ulceration of the entire colon, with involvement of the terminal ileum (an apparent progression of the disease to the small bowel since operation).

The patient was given ACTH (National) for 6 months, during which ileal and rectal discharge decreased considerably, and she experienced subjective improvement. She gained 9 kg. X-ray and sigmoidoscopic visualization, however, showed no significant change, and total colectomy, with resection of the terminal ileum, was performed in February, 1952. Pathological examination of specimens from both large and small bowel disclosed extensive alterations consistent with long-standing active ulcerative enterocolitis. She withstood the extensive operation remarkably well and, 1 year later, was entirely well, with a well functioning ileostomy.

This patient was treated to observe whether ACTH might modify the inflammatory process in an isolated or sidetracked colon. Although symptomatic improvement was obtained and she was improved as a surgical risk, treatment with ACTH did not alter the pathologic process. The surgical specimens, in the opinion of the pathologists, were typical of long-standing active ulcerative enterocolitis. There was nothing to suggest that the histologic abnormalities had been altered by ACTH or cortisone.

Case 4. S. J. (U186175), a 74-year-old barber with segmental ulcerative colitis of 3 months' duration, was treated with cortisone and ACTH almost continuously for 16 months, starting in January, 1951.

During this period he felt well, had minor flare-ups of bowel symptoms, but was able to lead a fairly active life. Barium-enema study in May, however, revealed that the process had extended to involve almost the entire colon. Sigmoidoscopy showed no significant change. In the fall of 1952, after the death of his son, he had a full recurrence of symptoms. Cortisone was again administered by mouth, with symptomatic improvement.

ess, as indicated by sigmoidoscopic (8 patients) and to a lesser extent x-ray examination (3 patients); in only 1 (Case 8), however, is the colitis now in clinical remission (Table 1). Apparent remission was observed in 1 patient (Case 2) four months after medication had been discontinued, but the subsequent

TABLE 1. *Summary of Results after Follow-up Study for One or Two Years.*

CASE NO.	FORM OF THERAPY	DURATION OF THERAPY (TOTAL)	IMPROVEMENT			RESULT OF 2-YR. FOLLOW-UP EXAMINATION
			SIGMOIDOSCOPIC EXAMINATION	X-RAY EXAMINATION	SYMPTOMATIC	
1	ACTH cortisone	10 mo. 5 mo.	+	+	+	Patient improved but with persistent disease*
2	ACTH cortisone	2 mo. 4 mo.	+	0	+	Remission?
3	ACTH cortisone	5 mo. 3 wk.	+	0	+	Patient improved but with persistent disease*
4	Cortisone ACTH cortisone cortisone cortisone	10 wk. 2 wk. 1 mo. 5 mo. 1 mo. (cont'd.)	0	0	+	Patient improved but with persistent disease*
5	ACTH cortisone	4 mo. 8 mo. (cont'd.)	+	+	+	Patient improved but with persistent disease*
6	ACTH cortisone cpd.f acetate cortisone	3 mo. 2 mo. 1 mo. 6 mo.	0	0	0	Patient improved but with persistent disease*
7	ACTH cortisone cpd. f ACTH	2 wk. 2 wk. 2 wk. 2 wk.	0	0	0	No effect; persistent disease.
8	ACTH	9 mo.	+	+	+	Remission?
9	Cortisone ACTH ACTH ACTH ACTH cpd. f ACTH	1 wk. 4 wk. 3 mo. 2 mo. 1 mo. 1 wk. 3 mo. (cont'd.)	0	0	+	Patient improved but with persistent disease*
10	ACTH cortisone cortisone	10 wk. 3 mo. 2 mo.	+	0	+	Patient improved but with persistent disease*
11	Cortisone ACTH	10 days 6 mo.	0	0	+	Patient improved but with persistent disease*
12	Cortisone ACTH cortisone	2 wk. 8 mo. 6 wk. (cont'd.)	+	0	+	Patient improved but with persistent disease*; continued treatment.
13	ACTH cortisone ACTH	4 mo. 7 wk. 3 mo. (cont'd.)	+	0	+	Patient improved but with continued disease*; continued treatment.

*Repeated or continuous therapy required.

In this case, the disease was acute and intermittent. Consistent symptomatic improvement was obtained as long as maintenance medication was continued. As in Case 6 the process in the bowel continued to extend, although the symptoms were suppressed by the hormones.

RESULTS

An impressive symptomatic response to hormonal therapy was attained in 12 of the 13 patients. All 12 gained weight, with a decrease in rectal discharges and cramps and an increase in appetite and strength. Some of these patients also gave parallel objective manifestations of improvement in the ulcerative proc-

follow-up period was too short to be conclusive. The remaining patients have required continuous hormonal treatment to maintain symptomatic suppression of what is apparently a continuing process. One patient (Case 7) did not respond to various preparations of ACTH or to cortisone or hydrocortisone. Contrary to expectations, patients with sigmoidoscopic or x-ray evidence of improvement did not experience a more lasting remission. Cases 1, 10 and 12 exploded abruptly into full-blown acute ulcerative colitis, although there had been symptomatic, sigmoidoscopic and roentgenographic evidence of a favorable response consequent to hormonal treatment.

Ten patients required continuous or intermittent treatment because symptoms recurred while the hor-

mone was being withdrawn or soon thereafter. These recurrences were not severe, responded promptly to increase in dosage or resumption of therapy and did not necessitate hospitalization.* In 2 cases resistance to ACTH developed after several months of treatment; a third was refractory from the start to several preparations. In these patients a close correlation existed between clinical improvement and adrenocortical stimulation induced by highly purified preparations of ACTH. The persistence of active disease, despite symptomatic improvement, was confirmed pathologically in 1 patient who underwent colectomy after six months of continuous and effective ACTH therapy.

Discussion

ACTH and cortisone suppress many of the manifestations of ulcerative colitis; in a number of cases they induced a symptomatic remission. If treatment is continued long enough, these agents occasionally have an anti-inflammatory effect, as indicated by sigmoidoscopic and, to a lesser extent, x-ray evidence of improvement and return toward normal. The pathologic process, even after many months of suppression, is not completely reversed; it continues to smolder, as shown by the abrupt recurrence of acute ulcerative colitis after hormone withdrawal in a number of our patients in whom the disease was effectively controlled by prolonged therapy. This phenomenon has its counterpart in the effect of ACTH and cortisone in rheumatoid arthritis, as described in a previous report.[12]

The clinical course of ulcerative colitis is variable and, to a degree, unpredictable. This fact has a bearing on the indications for and the results of corticotherapy. Two general clinical types are commonly encountered. The first is characterized by persistent low-grade bowel and systemic symptoms, associated with periodic and recurrent flare-ups. Each flare-up accelerates the progression of a slowly worsening pathologic process. Cases 1, 9 and 10 are examples of this type. It was possible to suppress the exacerbations in these patients quite successfully; although the disease could not be entirely cured at least the overt manifestations were controlled. Whether the well known complications were prevented and the rate of progression decelerated by this method of treatment is, of course, a matter of conjecture. Since the degree of deterioration is roughly proportional to the intensity of the disease it seems reasonable to assume that complications and progressions are minimized if the inflammatory process is controlled.

The second type is characterized by a progressive course and continued bowel and systemic symptoms. It has been our experience that the more numerous the symptoms and signs of the disease, the more effectively corticotherapy seems to suppress them — in other words ACTH and cortisone can be expected to have an anti-inflammatory effect, but cannot be expected to modify structural alterations in the bowel. In patients with chronic, active disease continuous treatment is usually required. If the daily dose of ACTH or cortisone that produces the desired response does not lead to serious cumulative metabolic effects continued therapy is feasible. In none of our patients was it necessary to terminate therapy because of serious metabolic or hormonal effects; in a larger series one would expect a certain percentage of treatment failure on this basis.

The present study raises more questions than it answers. Does long-term corticotherapy suppress the illness and hold the pathologic process in abeyance? Does it prevent stricture, hemorrhage and perforation? Does it suppress the inflammatory process sufficiently to make the difference between a salvageable and a nonsalvageable colon? If long-term therapy, as defined in this study, suppresses the disease will more protracted treatment ultimately cure it? Study of such a small number of patients does not give the answers; extension of this and similar investigations may do so. We intend to continue this study until the issue in each case becomes clear. The future probably holds one of five possibilities for each of these patients: a hormone-induced remission; a spontaneous remission; a progressive course, despite adequate hormonal treatment; a partial remission of ulcerative colitis at the exorbitant price of serious metabolic effects; and a progressive course complicated by serious metabolic effects. The results to date certainly warrant a continuation of the present study; so far there has been a net gain, with no serious complications except the psychosis experienced by 1 patient (Case 9).

All patients, except for the 1 who failed to respond, considered themselves greatly benefited and desired to continue treatment indefinitely. A few were restored from a state of chronic invalidism to good health; others were spared ileostomy and colectomy. In general it can be said that a disease known and feared for its serious medical, social and economic implications was temporarily controlled although not mastered.

The complete lack of effect in Case 11, as determined by histologic examination, and the extension of the process in Cases 4 and 6 are phenomena that, if supported by future study, may more accurately define the fundamental value of the hormones. It should be emphasized that pronounced symptomatic improvement can be expected in most cases. The symptomatic response, however, may not be accompanied by regression of the ulcerative or inflammatory process. It is nevertheless encouraging that in some patients sigmoidoscopic and x-ray examination showed improvement; the frequent recurrences during or after withdrawal of the hormone, even in these patients, clearly indicated that the disease was controlled temporarily but not cured.

*Since this report was prepared for publication, a severe withdrawal exacerbation in 1 patient has been only partially controlled by massive doses of cortisone and hydrocortisone (400 mg. of cortisone acetate daily by intramuscular injection and 400 mg. of hydrocortisone—free alcohol—daily, in 6 divided oral doses). An ileostomy was eventually performed, and the patient (Case 6) died as a result of perforation of the ileum and generalized peritonitis.

In several cases in this study a relapse of the disease and a lessening of the secondary effects of adrenocortical-hormone production were observed despite continued administration of previously effective doses of ACTH. Prolonged hyperstimulation of the adrenal cortex by potent preparations could conceivably exhaust the adrenal glands. Our studies in these patients, however, showed that the clinical relapse was due to resistance to ACTH rather than to adrenal exhaustion. This is in agreement with the findings of other workers,[13] who report that adrenal unresponsiveness, as manifested by insignificant eosinopenia and urinary 17-ketosteroids, occasionally follows continued administration of relatively crude ACTH. This phenomenon has been attributed to tissue inactivation rather than to the formation of antihormones. ACTH prepared by extraction with glacial acetic acid and purified by absorption elution on cellulose is more resistant to tissue inactivation, or at least does not lead to a local, species-specific sensitivity phenomenon. The more purified preparations employed in the latter part of this study (Wilson ACTH gel, Armour H.P. gel, National ACTH) did not result in resistance to ACTH, even after twelve or more months of continuous administration.

Adrenal exhaustion, then, is only a theoretical possibility. Periodic use of cortisone, which appears equally effective in maintenance therapy, seems a rational solution to this theoretical problem. On the other hand, depression of endogenous ACTH production by prolonged use of cortisone can be reversed by intermittent alternation of ACTH and cortisone.[14]

Standardization of initial or maintenance doses of ACTH and cortisone, like that of other hormones, is apparently impossible. Our procedure has been to give sufficient doses for a desired effect and then to reduce or discontinue the medication while attempting to maintain this effect.

Summary and Conclusions

Thirteen patients with ulcerative colitis were given prolonged treatment with ACTH and cortisone.

Treatment resulted in a satisfactory remission in 1 patient. Remission probably occurred in another although the follow-up period was too short to be conclusive. One patient with long-standing disease, extensive cicatrization of the colon and low-grade bowel and systemic symptoms did not respond to treatment. In 1 case in which colectomy was performed because of a pre-existent ileostomy an excellent symptomatic remission occurred, despite active inflammatory disease in the colon. Two patients had roentgenographic or sigmoidoscopic evidence, or both, of progressive disease although they showed appreciable symptomatic improvement.

The remaining 7 patients have required either continuous or repeated treatment to maintain improvement. Long-continued suppressive therapy made possible a return to normal life and gainful occupation in spite of the persistence of low-grade, active disease.

No complications of ulcerative colitis, such as stricture, hemorrhage and perforation, were encountered. No complications directly attributable to the metabolic effects of ACTH and cortisone were noted, except for an episode of severe psychosis in 1 case.

The therapeutic response followed a definite pattern. Symptomatic, sigmoidoscopic and roentgenographic evidence of subsiding disease occurred in that order of frequency.

Extension or continuation of the process, masked completely by a sense of well-being and by suppression of diarrhea produced by the hormones, can be determined only by sigmoidoscopic and x-ray examination.

The close correlation between clinical improvement and adequate adrenocortical stimulation in patients treated with ACTH has important practical implications. It contributed materially to our conviction that the favorable response is indeed related to the anti-inflammatory effects of the hormones and not to a nonspecific placebo effect. One must be certain that the conclusion, relapse in spite of continued ACTH therapy, is not actually one of relapse because of the development of ACTH resistance. The long-acting ACTH gels now commercially available (ACTHAR H.P., Wilson gel, National ACTH) did not appear to lose potency or effectiveness with long-continued administration.

Prolonged treatment, as described in this study, does not cure ulcerative colitis. Until other, more effective measures are developed the prolonged use of ACTH or cortisone seems to offer more than any other single form of therapy. Further studies are necessary to ascertain whether the end result represents a net gain or a net loss. Additional work is also needed to determine whether a multipronged attack — for example, combined use of corticotherapy, psychotherapy and antibiotics — will alter the natural course of the disease. This study has demonstrated that ACTH and cortisone have a favorable effect on ulcerative colitis; it has not shown that the natural course of the disease is significantly altered by their use.

We are indebted to David Klein, Ph.D., Wilson Laboratories, for the Wilson ACTH gel, Elmer Alpert, M.D., Merck and Company, for the Cortone and Hydrocortone, William Swain, National Drug Company, for the National ACTH, and to Armour Laboratories for the ACTHAR, ACTHAR gel and ACTHAR H.P. gel.

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USE OF SEPARATED HUMAN RED CELLS*

A Report of Current Practice and Progress

JOHN G. GIBSON, II, M.D.†

BOSTON

DURING the last decade the use of preserved whole blood has become accepted practice. The majority of hospitals now operate blood banks, obtaining blood from the American National Red Cross or by individual recruitment. The standard collecting solution is acid citrate dextrose (ACD),[1] which has preservative qualities sufficient to permit safe usage of properly refrigerated whole blood up to twenty-one days.[2]

ACD blood differs significantly from the normal in several important respects. Since it is a diluted blood one must infuse a volume of 575 cc. to administer the components of 500 cc. of blood. The solution contains 16.8 milliequiv. of sodium, increasing the total sodium administered. It is a highly acid blood. The initial pH of the plasma is 7.0 and since red cells continue to metabolize during storage, producing fixed acids, the pH progressively falls, reaching levels of 6.6 at about fifteen days and 6.5 at twenty-one days of storage. Potassium diffuses out of the red cells, plasma levels rising to 20 milliequiv. per liter at twenty-one days.[3] The citrate ion is present in excess of the amount needed to complex calcium and may produce a functional hypocalcemia in cases of hepatic disease,[4] through failure of catabolism of citrate, and in exchange transfusions of erythroblastotic infants.[5] These qualities are characteristics of the plasma, and the burden they impose when whole ACD blood is given may be avoided by the use of separated red cells only.

GENERAL CONSIDERATIONS

In contrast to progress made in whole-blood transfusion, as well as that of plasma and its derivatives, little use has been made of separated red cells. During World War II and the Korean action large quantities of citrated blood were collected to obtain plasma for drying and fractionation, and virtually all the cells from this blood were discarded. Failure to utilize at least some portion of the cells collected can be attributed to three factors.

The Anticoagulant Solution

Blood was collected in vacuum bottles containing 50 cc. of 4 per cent sodium citrate, an alkaline solution. No dextrose was added. The rate of utilization of dextrose by red cells at the resultant pH of 7.4 was high, and the absence of supplementary sugar resulted in a rapid rate of deterioration of the cells.

Transportation and Refrigeration

Usually, from twenty-four to forty-eight hours elapsed between collection and removal of plasma. Ambient temperature of containers varied from 0 to 10°C. During this interval the degree of deterioration of the cells was severe. Restoration to conditions known to be optimal for fresh cells was necessary to protect viability. This could be accomplished only by resuspension of centrifuged cells in a preservative medium.

Since plasma was processed at laboratories at some distance from the collection centers distribution of separated cells involved a further transportation problem.

Equipment for Collection and Separation

The removal of plasma and addition of resuspension fluid required entry into the original container, involving a risk of bacterial contamination.

Braude et al.[6] found the rate of contamination of bloods sampled at some time between collection and transfusion was 4.5 per cent, in contrast to a rate of 2.24 per cent in bloods cultured at the time of collection, in which airborne contaminants predominated. Pittman[7] recently called attention to the importance of nonpathogenic organisms in causing serious and often fatal reactions, notably certain species of pseudomonas

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and of the coli-aerogenes group, which go on at blood-storage temperatures.

This possibility that the outer surface of blood containers will become contaminated with such psychrophils exists, and the accidental introduction of these organisms in sampling procedure constitutes a far more serious hazard than that posed by airborne contamination during routine blood collection.

The choice of anticoagulant, transportation and the lack of a reliable sterile system for separation of components rendered distribution of cells on a large scale thoroughly impractical. Nevertheless, during World War II two successful programs for distributing cells from citrated blood collected by the American Red Cross were carried out.

Cooksey and Horowitz[8] reported the distribution of 1000 bottles of citrated cells to fourteen hospitals in the Detroit Area in 1941-1944. Group O cells were resuspended in 0.85 per cent sodium chloride in the original bottle within twenty-four hours of collection. An aseptic manual technic was used, and sterility checked by culture. Reaction rates were lower than those encountered with whole blood. Improvement in hemoglobin and red-cell counts of recipients was noted.

Thalhimer and Taylor[9] resuspended citrated cells in 10 per cent corn syrup, employing an aseptic manual technic and distributing cells in the original bottle. They reported on 761 infusions in 347 patients in 1945. The reaction rate was comparable to that observed with whole blood. Clinical results were satisfactory, and studies by the Ashby agglutination technic indicated a safe dating period of at least ten days. These results were confirmed by me and my associates in 1945.[10]

These successful clinical trials clearly indicated that citrated cells could be used provided that processing was carried out within twenty-four hours of collection, refrigeration was optimal and asepsis was maintained.

Clinical Application

This paper is an attempt to summarize available information on the safety and practicability of the clinical use of sedimented, packed or resuspended human red cells. Experimental and clinical reports have been drawn on as a basis of determining existing possibilities. The limitations of present practices are commented on as background for a presentation of current developments designed to simplify and safeguard procedures.

Several factors stress the need for a consideration of practical methods at present. Chief among these is the necessity for full economy of available human resources, particularly sharpened by the recent decline in public response to appeals for blood donations at both the community and the national level. Secondly, there is a growing appreciation of clinicians of the therapeutic value of separated red cells. Thirdly, it is possible that the virus of homologous serum jaundice can be rendered noninfective, thereby permitting resumption of large-scale collection of blood for plasma with a resulting huge supply of residual red cells. And, finally, there is a possibility of better preservation of separated cells, particularly in the frozen state, than is currently obtained with whole blood.[11,12]

The limiting factor of anticoagulant solution has potentially been removed by the recommendation of the National Research Council made at a meeting of the Committee on Blood and Related Problems on October 29, 1953, that all blood should be collected in ACD. This could ensure that cells are protected by immediate exposure to the known optimal extracellular environment for preservation. This recommendation was based, in part, on the demonstrated suitability of ACD plasma for drying or fractionation.

The second limitation—namely, the transportation period—is mitigated somewhat by the use of ACD and could be eliminated completely by the practice of separating blood in the collection centers.

Trials are currently under way at the Regional Blood Donor Center of the American National Red Cross at Washington, D.C., in which red cells separated from ACD blood will be distributed for clinical use in local hospitals.[13]

The third limitation, the risk of bacterial contamination in processing, remains a serious obstacle, and limits the infusion of cells to a period much shorter than their true cell-replacement value.

In recent years a great deal of thought and effort has been spent on the development of apparatus and procedures for providing closed sterile systems for collection and separation of blood into its components and for resuspension of cells. Basic considerations have been the development of mechanical devices to supplant previous manual operations and the employment of automatic controls to eliminate mistakes due to human judgment.*

An apparatus developed by the late Dr. Edwin J. Cohn and his associates in the University Laboratory of Harvard University is shown in diagrammatic form in Figure 1. It is adapted to the collection of blood either in ACD or through an ion-exchange resin.[14]

Sterile, pyrogen-free ACD is run into the revolving bowl of the centrifuge. Blood flows directly from the donor through a heat exchanger into the centrifugal field in the bowl. It becomes mixed with the ACD solution, and under centrifugal force, the heavier red cells migrate to the periphery, displacing the plasma toward the axis of the bowl. The retaining capacity of the bowl and centrifugal force applied are such that the bulk of the plasma from one donation of blood flows out and is collected through an outlet into a sterile container, leaving the cells in the still revolving bowl. Reduction in centrifugal force permits the cells to flow out and to be collected in another sterile container.

*I have had the opportunity to study the characteristics of red cells processed by the apparatus developed by both Dr. Cohn and Dr. Walter and gratefully acknowledge their co-operative collaboration.

When an ion-exchange resin is used as anticoagulant blood flows from the donor through the resin column, through the heat exchanger and directly into the bowl, separation and collection proceeding as described above.

The apparatus is designed so that all parts with which blood comes in contact may be sterilized as a unit. Units can be used again. Recent tests have demonstrated that complete asepsis is possible.[15]

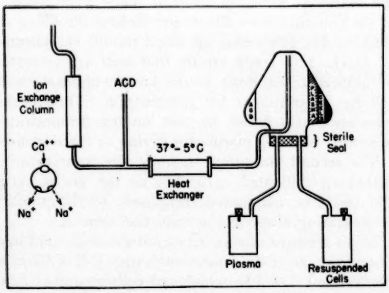

FIGURE 1. *Diagrammatic Sketch of Biomechanical Equipment for Separation of Blood into Components (Developed in the University Laboratory of Physical Chemistry Related to Medicine and Public Health of Harvard University). The apparatus is adapted to collection of blood either in ACD or through an ion-exchange resin.*

Although no clinical trials of red cells separated in this machine have as yet been made, in vitro studies indicate that no significant damage to the cells occurs in the separation. Figure 2 shows the characteristics of cells separated in this apparatus from blood collected through a cation-exchange resin, XE-132, and resuspended in Buckley's solution.*

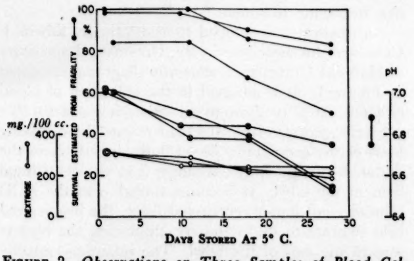

FIGURE 2. *Observations on Three Samples of Blood Collected through a Mixture of Cation-Exchange Resins on the Sodium and Hydrogen Cycle in the Biomechanical Equipment Developed in the Harvard University Laboratory.*

*Buckley's solution has an electrolyte pattern approximating that of normal plasma, is buffered to a pH of 5 with sodium citrate and citric acid, and has a dextrose concentration of 600 mg. per 100 cc.

Survival estimated from osmotic fragility tests, the utilization of dextrose and the fall in the pH of the plasma are about the same as those observed in cells from blood collected through another resin, Dowex-50, and resuspended in Buckley's solution. The viability characteristics of those cells, determined in vivo by the Ashby method, are shown in Figure 3. Cells from blood collected through XE-132 probably have a safe dating period of at least ten days, a value that must be confirmed by both in vivo and clinical tests.

The system developed by Dr. Carl W. Walter, of the Department of Surgery, Harvard Medical School, and his associates at Fenwal Laboratories, Framingham, Massachusetts, is described in Figure 4.

Blood is collected in a plastic bag containing pyrogen-free, sterile ACD. The bag is centrifuged by means of standard equipment. Withdrawal of plasma is effected by application of external pressure to the bag in an electronically controlled press. Both the plasma outlet port of the bag and the piercing needle in the tube of the collection pack are mechanically protected by sterile sheaths. High-intensity, bacteriocidal ultraviolet radiation bathes the channels exposed to blood as they are mechanically coupled. The plasma is extruded by continuous pressure, flow being stopped automatically by a photoelectric-cell-activated mechanism when the packed red cells enter the outlet tube, thus preventing admixture of cells with the extruded clear plasma. Plasma can be collected either in individual packs (group specific) or pooled. Devices are provided for dielectric sealing of the tubes. Both red-cell and plasma packs have an integral aliquot for cross-matching and culture.

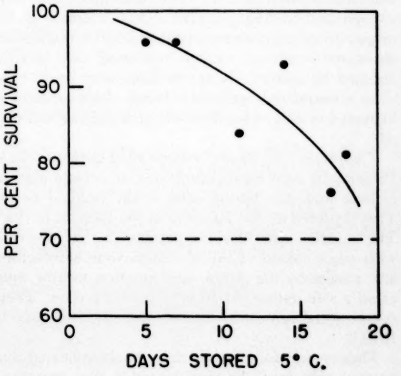

FIGURE 3. *Postinfusion Survival of Cells from Six Blood Samples Collected through a Cation-Exchange Resin, as Determined by the Ashby Differential Agglutination Method. The line at 70 per cent survival indicates the lowest level of survival compatible with a safe infusion.*

The bag with the packed cells is removed from the extrusor, with the piercing needle in place; a seal is placed proximal to the point of exit, and the needle and tube separated from the bag. The cells thus remain in the original container in which they were collected for storage and transportation and from which they may be infused through a second sterile outlet port. If it is desired to resuspend the cells further application of pressure extrudes them into a bag containing sterile, pyrogen-free solution.

This device, designed for extrusion of plasma without reference to salvage of red cells, was successfully used by Sharp and Dohme[16] on 7000 blood samples collected by the United States Army at the Blood Donor Center at Indian Town Gap in 1952-1953. During this trial cells from 56 consecutive blood specimens were resuspended in Buckley's solution, an improvised technic being used for addition of the solution to the cells in the original container. Sterility tests showed no contamination of any of the resuspensions at periods ranging from three to twenty-nine days after processing.

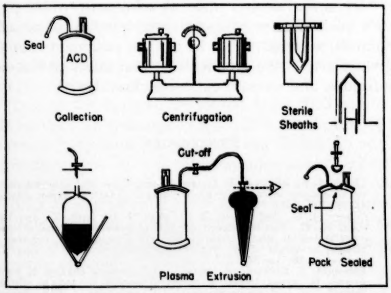

FIGURE 4. *Procedure in Separating Red Cells from Plasma of ACD Blood in the System Developed by Fenwal Laboratories.*

The viability characteristics as judged by in vitro evidence are shown in Figure 5. It seems warranted to conclude that the cells processed at Sharp and Dohme could have been safely and beneficially infused for fourteen days after separation.

In vivo studies of ACD cells resuspended in Buckley's solution, the radiochromium method of measuring survival being employed, are shown in Figure 6. The data indicate that clinical trials, infusing cells stored up to twenty-one days after resuspension, are warranted.

It should be noted that cells of ACD blood collected in the type of plastic containers used in both devices described above are preserved as well during refrigerated storage as those of ACD blood in glass.[17]

It has been known since 1947 that the viability characteristics of cells of blood collected in ACD, separated by centrifugation and stored under refrigeration as packed cells are equal to those of ACD cells stored as whole blood.[2,18] It has also been observed that the net increase in total blood volume resulting from transfusion is due to the retained red cells, most of the fluid given as plasma leaving the blood stream within twenty-four hours.[19]

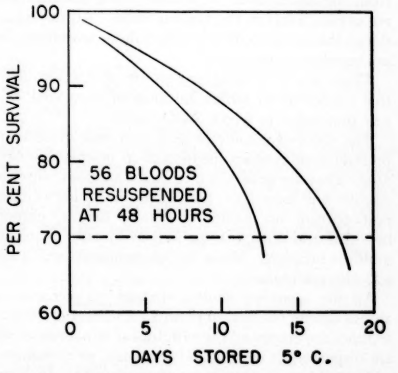

FIGURE 5. *Range of Survival Estimated from Fragility Tests of 56 Blood Samples Collected in Sodium Citrate at Indian Town Gap, Resuspended in Buckley's Solution after Removal of Plasma in the Fenwal Extrusor and Shipped to Boston under Refrigeration.*

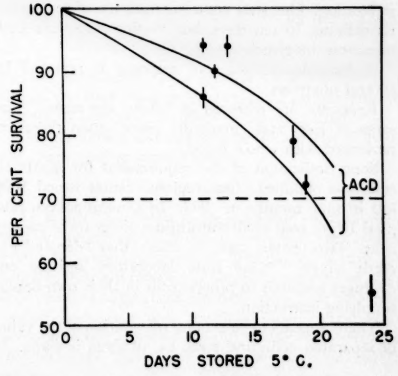

FIGURE 6. *Postinfusion Survival of Red Cells from 7 Blood Specimens Collected in a Modified ACD Solution, Resuspended in Buckley's Solution after Removal of Plasma, as Determined by a Radioactive Chromium Technic.*

These basic considerations, therefore, define the indications for the administration of separated red cells.

Discussion

I recently requested information on current opinion and practice regarding the use of separated red cells from the directors of twenty-one blood banks in representative areas in the United States. All the replies stated that separated cells had definite usefulness and are supplied as requested.

There was a striking uniformity of opinion about the conditions in which infusion of separated cells was preferable to whole ACD blood.

The reduced volume of separated cells made them preferable in cardiac disease and in infants and children. They are generally used in the anemias: chronic, aplastic and hemolytic, and those due to hemorrhage post partum or during operation, cancer, chronic nephritis and leukemia, as well as in cases requiring multiple infusions. Value in "plasma-sensitized" cases was also maintained.

All the reporting centers stressed maintenance of asepsis during removal of plasma. A variety of manual technics are employed for withdrawal of plasma. Cells are dispensed in the original container, or transferred with sterile precautions to another container. In many centers plasma is pooled and stored frozen.

Most centers prefer to use cells as packed by centrifugation and encounter no difficulty in administration. When resuspension is employed saline or dextrose and saline solutions are commonly used. One state center resuspends in 10 per cent corn syrup.

Immediate use appears to be the general rule, usually within twenty-four to forty-eight hours after separation. This short period is deemed necessary because of the danger of contamination incident to separation. One state center permits use of resuspended cells up to ten days, but routinely cultures each bottle on thioglycolate at 32°C.

A favorable hemoglobin response is reported by several observers.

Reactions are reported as "about the same," "the same or less" and "markedly lower" than those experienced with whole blood.

Some indication of the requirement for separated cells was obtained. One regional center issued 1000 lots in nine months in 1953. In a metropolitan hospital 10 per cent of all transfusions given are of packed cells. Two centers state, in effect, that "demand exceeds supply." One state laboratory actively encourages hospitals to process cells in their own banks, supplying instruction.

There appears to be general recognition of the value of separated cells, and some use of them is made. It is evident that greater utilization of cells is limited principally by lack of knowledge of the safe infusion period and the risk of contamination imposed by the manual methods employed for lack of better technics.

Conclusions

Red cells separated from ACD blood by sedimentation or centrifugation have viability characteristics permitting safe infusion for at least fourteen days after collection.

The clinical value of red-cell infusions in replacing red-cell-volume deficiencies has been amply demonstrated.

From 10 to 30 per cent of present hospital transfusion requirements could be met with separated cells.

Currently employed methods of separation involve a risk of bacterial contamination that limits the use of cells to a few hours.

Mechanical devices under development, which provide maintenance of asepsis and employ automatic controls to avoid errors in human judgment, should greatly extend the practicability and safety of red-cell infusions, and warrant extensive clinical trial.

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BENIGN (FAVORABLE) TYPES OF BRAIN TUMOR*

The End Results (up to Twenty Years), with Statistics of Mortality and Useful Survival

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IN 1941 a review of a series of 400 verified brain tumors was made, with certain statistics of useful survival of patients who had what were termed favorable tumors.[1] This favorable group at that time represented a little more than half (56 per cent) of the whole number of tumors, and it was found in the follow-up studies that 71 per cent of patients with one of these benign new growths had been able to lead useful lives from one to eight years after the removal of the tumors. This review in reality was little more than a preliminary report, since the total number of patients was not large, and the follow-up period in many cases was less than five years — the usually accepted period for giving so-called "end results." For these reasons it has appeared worth while to gather further data on brain tumors over a much longer interval.

During the twenty-year period from 1933 to 1952 inclusive 1718 patients with verified intracranial tumors were operated on at the Lahey Clinic. In addition there were 96 with pituitary adenomas "verified" by roentgenologic evidence of a greatly enlarged sella turcica as well as optic-nerve atrophy and visual-field defects. Patients in this group were not operated on, having responded well to x-ray therapy. The total number of tumors, therefore, is 1814.

Of this total number 862 were termed favorable — that is, most of them were completely removed at operation, the survivors living up to twenty years. This favorable group also included the pituitary adenomas given x-ray therapy, and a certain number of other cases in which the growths could not be removed completely but the patients have lived for five years or longer, for the most part in a useful capacity. More details on these patients are given in the discussion of the appropriate groups.

The tumors that for the most part could be wholly eradicated by surgical excision were the meningiomas, acoustic neuromas, many of the pituitary adenomas, the cerebellar astrocytomatous and hemangiomatous cysts, a large group of cerebral hemangiomas and a miscellaneous group including cholesteatomas, colloid cysts, some of the craniopharyngiomas and other less common neoplasms.

Among the new growths that could be radically although incompletely removed were certain cerebral astrocytomas, a few oligodendrogliomas and again a small miscellaneous group. The patients survived and lived useful lives for at least five years and in many cases much longer.

The varieties of tumors represented in this report, together with the number of each type considered favorable according to the standards set forth, are shown in Table 1. Nearly half (47.5 per cent) of the brain tumors in the series may be regarded as favorable with the probability of a good prognosis from five to twenty years. This figure is somewhat less than the 56 per cent reported in 1941, but probably more correct in view of the longer follow-up period.

TABLE 1. *Types of Brain Tumor.*

CLASSIFICATION		No. OF CASES
All tumors:		
Verified		1718
Pituitary (verified by x-ray study etc.)		96
Total		1814
Favorable tumors:		
Meningiomas		259
Pituitary adenomas found at operation		147
Pituitary adenomas verified by x-ray study etc.		96
Acoustic neuromas		120
Hemangiomas		82
Cerebellar	48	
Cerebral	34	
Astrocytomas		67
Cerebellar	35	
Cerebral	32	
Craniopharyngiomas		20
Cholesteatomas		15
Oligodendrogliomas		11
Miscellaneous		45
Total		862 (47.5% of total 1814 tumors)

Certain details and statistics of the various individual types deserve consideration.

MENINGIOMAS

As might have been expected these encapsulated, usually accessible growths represented the largest group of benign intracranial tumors. With rare exceptions they are capable of complete extirpation, and with modern adjuncts of electrosurgery, carefully controlled anesthesia and multiple blood transfusions when necessary, single-stage procedures have replaced the two-stage operations frequently used in earlier series.

Meningiomas represent 13.9 per cent of the whole series and 28.6 per cent of the favorable tumors. There were 35 deaths among the 259 patients with this type of tumor, a mortality of 13.5 per cent.

There were 183 patients with meningiomas who were operated on before 1948, and it is from this

*Amplification of a paper read at the Fifth International Neurological Congress, Lisbon, Portugal, September 7-12, 1953.
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group that statistics of five to twenty years may be derived. Of the 159 survivors, it is known that 129 lived from five to twenty years, with 16 not heard from. All but 6 of these patients were living useful lives at the last report, representing 77.3 per cent of the survivors. Of the whole group of 259 there were 181 who lived useful lives for one year or longer.

Pituitary Adenomas

The group of pituitary tumors includes 147 patients whose adenomas were verified by operation and 96 in whom the diagnosis was made by the presence of a large, "ballooned" sella turcica together with visual-field defects and optic atrophy (these patients were given x-ray therapy only).

There were 129 pathologically verified chromophobe adenomas and 18 of the chromophil variety. Eighteen patients in this combined group died after the primary operation, giving a 12.2 per cent operative mortality. As stated in a previous publication,[2] however, this high mortality was attributable entirely to the large number of patients who had considerable extensions of the tumor into the intracranial cavity. Among those who did not have such extensions the mortality was 3.9 per cent. This agrees with the experience of Jefferson[3] and of Bakay[4] (Olivecrona's clinic).

All the patients with adenomas were operated on by frontal craniotomy, a radical removal of the tumor being accomplished in nearly every case. Only 8.6 per cent of the patients died within five years of recurrence, whereas the five-year mortality after the old transphenoidal method was reported as 32.3 per cent by Henderson[5] (Cushing's patients) and as 19.8 per cent by Hirsch.[6]

Other interesting facts related to the treatment of pituitary adenomas are the following. Of the 147 patients whose tumors were removed surgically 45 (30.6 per cent) had to be operated on because x-ray treatment had not been effective, whereas only 11 patients (7.4 per cent) received irradiation because of tumor recurrence after operation. However, for the past four years, during which the patients have been treated by the 2,000,000-volt x-ray apparatus at the Massachusetts Institute of Technology, the results of this therapy have been so good that the necessity for operation has been the exception rather than the rule.

Useful life may be judged, in patients with pituitary adenomas, largely by the improvement in vision or the maintenance of useful vision.

In the 147 operative cases 116 patients were operated on before 1948 so that a five-year follow-up report is available. Of these, 71 (61.2 per cent of the total 116, or 70 per cent of the 101 survivors) were in useful life five years or more after operation. Of the whole group of 147 patients there were 82 who engaged in useful activity for one year or more.

Acoustic Neuromas

Of the 120 patients with unilateral acoustic tumors in this series 16 died after operation, giving an operative mortality of 13.3 per cent. Fourteen of these patients had been operated on one or more times elsewhere, making the procedure of complete removal extremely hazardous. There were likewise 5 patients operated on before 1934 who had only "intracapsular" removal of the tumor.

In the remaining 101 patients the tumors were completely removed, and there were 11 deaths in this group, giving a present-day operative mortality for the past nineteen years of 10.9 per cent. During the last five years the facial nerve has been spared in about a fifth (20 per cent) of the cases.

Of the whole group of 120 patients there were 104 who survived operation, and 75 of these (72 per cent), have been living useful lives up to twenty years after operation.

Hemangiomas

Cerebellar

These tumors, especially when they are partly cystic, are one of the most favorable varieties of brain tumor, a point that has been emphasized by many writers. The so-called mural nodule may be only a few millimeters in size, or it may be a large, solid tumor partly surrounded by a relatively small cystic area. There were 48 cerebellar cystic hemangiomas in this series, with 7 operative deaths, a mortality of 14.5 per cent. Of the 48 patients, 4 had associated hemangiomas of the retina (Lindau's disease).

Thirty-five of the 48 patients have been in useful life up to twenty years after operation. This represents 73 per cent of the total number, but 85.3 per cent of the 41 survivors.

Cerebral

Although any patient with a tumor above the tentorium may be subject to epileptic seizures, the cerebral hemangiomas on the whole represent a favorable type of growth. Among the 34 patients in this category there were 4 operative deaths, a mortality of 11.7 per cent. Twenty-one (61.7 per cent) of the total 34, or 77.7 per cent of the 27 patients who lived five years or more, were living useful lives.

Astrocytomas

Cerebellar

Like the hemangiomatous cysts in this situation the astrocytomas of cystic type below the tentorium are among the most favorable intracranial tumors. There were 35 such patients in this series, 3 patients having died after operation, a mortality of 8.5 per cent. Twenty (57.1 per cent) of the total 35 patients were

in useful life up to twenty years after operation. Among the 32 survivors 2 died within two years, and 5 have not been heard from; therefore, the 20 in useful life represent 80 per cent of the 25 on whom data are available.

Cerebral

In the whole series of brain tumors there were 314 astrocytomas situated above the tentorium. Although histologically many of them can be classified as slowly growing, relatively few can be called truly benign or favorable growths from their clinical course. Although my follow-up records on this group are as yet incomplete it appears that about 10 per cent of all the cerebral astrocytomas have come into the favorable category—that is, the patients who have lived from five to twenty years, for the most part without serious complaints.

Of the 32 patients who lived over five years, 5 died between five and nine years after operation. Of the remainder 21 have lived useful lives for five to seventeen years. This represents 65.6 per cent of the total 32 patients.

Craniopharyngiomas

These congenital cysts, arising from rests of Rathke's pouch, on the whole are not favorable either from the operative point of view or from the standpoint of survival in useful life. Of the 48 such cysts in the series, all the data indicate that 20 should be classed as favorable for removal. Among these 20 there were 7 operative deaths, a mortality of 35 per cent, which were due largely to disturbance of the hypothalamic area, with subsequent hyperthermia. Of the 13 survivors only 6 (46.1 per cent) can be considered as living useful lives.

Oligodendrogliomas

Although the majority of these tumors are malignant a small number of patients with oligodendrogliomas survive a radical extirpation of the growth for long periods and live useful lives. There have been 11 such patients out of a total of 31, and they have been followed for five to thirty-three years,* for an average of twelve and seven-tenths years. Ten patients (90.9 per cent) lived useful lives for five years or more, and 1 is still living in perfect health twenty years after the original operation.

Miscellaneous Tumors

Under this heading I have grouped a number of the extremely unusual types of growth, together with the cholesteatomas, colloid cysts of the third ventricle and some of the pinealomas. Among the 60 patients with favorable miscellaneous tumors there were 6 operative deaths, a mortality of 10 per cent. Forty-five of the 54 survivors (83.3 per cent) have lived useful lives for periods up to twenty years.

*The patient who lived thirty-three years was operated on twice by Dr. Harvey Cushing, and three times by me, the first operation having been performed in 1916.

Discussion

There are relatively few reports in the available literature of large series of brain tumors with reference to long or useful survival or both. From Eisenhardt's[7] statistics of Cushing's 2000 patients, about 31 per cent of approximately 1600 survivors had lived for five to twenty-eight years at the time of this report in 1935. This figure would doubtless be considerably higher after a further interval. The question of useful survival was not considered in detail in this paper, except for the patients whose case histories were given.

Davidoff,[8] in 1940, studied the end results in 457 patients operated on by Cushing fourteen to sixteen years previously. Thirty-seven per cent of these patients lived from seven to fourteen years, and it may reasonably be estimated from the data given that 21 per cent of the whole group, or 57 per cent of the 170 survivors, had lived useful lives.

Figures given by Grant[9] in 1951 on 802 patients with brain tumors indicated that 238 (29.6 per cent) had survived five years or more, and of these survivors 173 (73 per cent) had lived useful lives for at least some portion of their survival. Grant's conclusion was that in a representative series of brain tumors about 40 per cent would be benign. In a subsequent paper in 1953 he[10] reported on a group of 1603 patients with brain tumor, 534 of whom had lived for five years or more. This figure, therefore, represents 33.3 per cent of the total 1603 patients, and 48.3 per cent of the 1107 who survived operation. Data on useful survival were given only for the patients with cerebral and cerebellar gliomas of the benign type, 78 per cent of whom had returned to work.

It is difficult and perhaps impossible from the studies just summarized to arrive at any absolute conclusions regarding the expected survival and especially the useful survival of the patients represented in the reports of these large series. In some cases data are incomplete, and in addition mortality rates vary to some extent so that statistics based on survival are not wholly comparable. What may perhaps be said is that roughly 30 to 35 per cent of the patients operated on had lived for five years or more, but if one considers only those who survived the operation, the expected five-year survival is about 50 per cent. Of these, a considerable proportion, probably 70 to 75 per cent, would be useful citizens for some portion if not all of their remaining lives.

Summary

In a group of 1814 intracranial tumors 862, or nearly half the total number, represented tumors that

should be termed favorable so far as operability* and a prolonged period of useful life are concerned. Included in this total were 96 patients with pituitary adenomas who were not operated on but were given x-ray treatment, with improvement.

Among the 862 patients with favorable tumors there were 766 who were operated on, with 96 deaths, making 670 who survived operation. These 670 and the 96 with pituitary adenomas treated by irradiation make a total of 766 patients who either survived operation or were relieved by x-ray therapy.

Of these 766 patients 592 have engaged in useful activities for one to twenty years—the majority for five years or more. This number represents 68.6 per cent of the original 862 patients and 77.2 per cent of the 766 who survived operation or were relieved by x-ray therapy.

If one considers only the patients operated on, there were 670 survivors, and of these, 496 have lived useful lives for the periods followed, a matter of 74.1 per cent.

To get a correct idea of the operative mortality in the series, I have deducted from the total 862 patients the 96 with pituitary adenomas who received only x-ray therapy, and also such tumors as the cerebral astrocytomas and oligodendrogliomas, since only the five-year survivals in these groups were considered and hence their mortality would be 0.

This leaves 723 patients available for mortality figures, among whom the 96 deaths occurred. This makes the case mortality 13.2 per cent for all patients with benign brain tumors dying in the hospital from any cause after operation.†

*All patients were operated on either by me or by my senior associate, Dr. James L. Poppen, except for occasional operations by junior members of the neurosurgical staff.

†The so-called operative mortality would be somewhat lower than this figure since some of the patients underwent more than one operation.

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SPECIAL ARTICLE

LABORATORY FACILITIES FOR THE PRACTICING PHYSICIAN*

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THE transition from house officer to practicing physician is a monumental and rude one. Not the least significant hazard is the changed relation of the clinical laboratory to the doctor. The house officer has taken for granted the battery of tests available in a hospital laboratory, resting comfortably on the support that their accessibility, reliability, interpretation and relative freedom from economic pressures provide. He has had no concern in the maintenance of the laboratory, its equipment, reagents, personnel, technics and morale or its rapport with the clinicians it serves. All this has been another's responsibility till he ventures into practice for himself. Whether practicing alone or as a member of a small group the clinician must concern himself with the intimate workings of the clinical laboratory that he uses if he is to make proper use and evaluation of the determinations it reports.

To establish even the most elementary of office laboratories is no mean undertaking. The employment of a single part-time technician introduces a major complication into the problems of office routine and acceptance by patients of a service that has been too long and too widely neglected in private practice. These problems and those mentioned above are briefly discussed here. The tests themselves and their uses, limitations and pitfalls have been adequately described elsewhere.[1-3]

Physical Layout

The laboratory need not be large if it is well planned, the existing floor space necessarily dictating its size. It will need a sink, adequate lighting, ventilation and work space, as well as enough room for the technician or doctor, the patient and a companion, and it must provide a modicum of privacy from other waiting patients. Ready access to a lavatory and a couch are also essential.

Artificial lighting has the advantage of constancy,

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which is important in colorimetric work. Fluorescent lamps will offset their initial cost by economy of operation. They should be situated over the work space rather than in the middle of the room. Strategically placed electric outlets will be necessary for the microscope substage lamp, centrifuge, photoelectric cell, hot plate and refrigerator. If they are located waist-high or immediately above the work space needless bending will be obviated.

Whereas a window with a view has esthetic advantages it may be inefficient in removing noxious odors, obligate companion to many examinations. Forced ventilation may prove a necessity, though a simple ceiling or wall vent may prove sufficient for free circulation of air.

Work Space

Laboratory work necessitates much getting up and sitting down. Counter-type work space is therefore desirable, about 36 inches from the floor, with the sink's rim at the same level and a high stool available for sitting up to the counter.

The sink need not be large, but a flat bottom is helpful, and the faucets should be at least 18 inches above its floor to permit the easy cleansing of pipettes, syringes and other apparatus. Hot running water is desirable, and a water suction pump is essential for the proper cleaning and drying of laboratory glassware.

Although only a small refrigerator is needed, it should be set on a platform to bring its contents waist-high or higher. Space under the platform may be made a repository for infrequently used and cumbersome equipment.

The surface area of the counter should be at least 60 inches wide and 30 inches deep for each person working in the laboratory. (A group might well employ two technicians whose time would overlap; if their time is to be used efficiently they must be able to keep out of one another's way.)

Shelving over the work space and elsewhere in the laboratory should be built with its specific purpose in mind. Eight-inch clearance and 4-inch depth are quite sufficient to accommodate most reagent bottles and provide more shelving area in the same wall space. A deeper and more substantial shelf over the sink will support larger bottles for standard solutions used in quantity. A book shelf should be close at hand.

Piped compressed air is a refinement but gas outlets will be desirable in the larger office laboratories.

Apart from the working space a table will be necessary for venipuncture materials, the reclining arm for venipuncture and the receptacle to receive blood or fomites, together with a chair for the patient. In the office of the physician practicing alone this may well have to be in the examining or even the consulting room. In any event provision should be made for the presence of a parent or companion for the patient's moral support. A chair should also be available to him against the eventuality of sympathetic syncope. Similarly, a couch should be not too distant for brief recovery from such episodes; it will have other office uses.

Privacy

The collection of urine, stool, vaginal secretions and so forth must be made easy and with a minimum of inconvenience and embarrassment to the patient and the doctor alike. To this end office planning should permit ready communication between examining room, laboratory and lavatory without necessitating exposure to the view of anyone in the waiting room.

Equipment

Table 1 lists the essential instruments that may form the basis of a small office laboratory. Together with the reagents included in Table 2, they will suffice for the clinical tests most frequently indicated in the course of the general practice of office medicine. A few of these items deserve brief comment.

The centrifuge must be of good quality, whether of the angle type or free-swinging with a sturdy protective jacket, and capable of 2500 to 3000 revolutions per minute. Hematocrit determinations done on an inferior centrifuge will be unreliable.

Photoelectric colorimeters are expensive, of intricate design and subject to easy deviation from standardization. Although they provide a high degree of accuracy when properly operated they are subject to many technical errors in the hands of the untutored. The widespread custom of using photelometers on the basis of standardizations made by the manufacturer is universally decried by clinical pathologists and most medical technologists. Such instruments have no place either in the practitioner's office or in any laboratory that does not employ a technician conversant with the mechanisms and peculiarities of these instruments.

The electrocardiograph is likewise a highly specialized instrument, and should be used only under the direction of a physician specifically trained in the inscription and interpretation of tracings. Technically, the instrument is subject to less caprice than the photelometer discussed above, and deviations from mechanical perfection of operation will be immediately obvious to the trained interpreter.

The instrument for measuring basal metabolic rates is not included in this list of laboratory impedimenta, since its legitimate uses are considered to be limited in general practice and the technic of performance is so refined that the infrequent occasion for these determinations would materially reduce its reliability. Similarly, the physical conditions requisite for the achievement of a truly basal state of the patient are difficult to provide in an office. The recording of the test in the home is likewise fraught with practical difficulties.

Specimen bottles and medicine droppers should

have readily identifying features, lest the wrong anticoagulant be employed or a dropper used in urinalysis find its way into a prescription bottle. Likewise, specimen bottles should be adapted to use in the home and the doctor's bag as well as in the office. This implies minimum size, sturdy construction and tight, firm stoppers, preferably of the screw-on type. Community laboratories, whether commercial or governmental, usually provide their own containers for mailing. The office laboratory should be well stocked with these at all times.

It seems superfluous to suggest that attention be given to assuring the availability of up-to-date textbooks till one reflects that the practicing physician starts his career with his medical-school textbooks, probably already seven or more years old and containing discarded, inferior and even inaccurate procedural material.

The introduction of new equipment and new procedures will serve the incidental purposes of giving a fresh look to the laboratory and a new interest to the technician.

Facial or toilet tissues and a covered refuse can are a courtesy certainly due and appreciated by the patient subjected to the intimate indignities contingent on a number of laboratory examinations. The unprompted provision of fresh perineal pads similarly displays thoughtfulness for the patient's comfort.

Laboratory Equipment for the Doctor's Bag

Many of the laboratory data necessary to private practice will be derived from patients confined to the home. Materials for the collection and transportation of specimens must be carried in the doctor's bag or car. Some highly significant tests can be performed at the bedside if a few simple reagents are included (notably, those for glucose, acetone or blood in the urine and for melena). Hemoglobin determination at the bedside is not feasible, the so-called Tallqvist method being totally unreliable.

Containers for many routine studies (urine, stool, sputum and so forth) can be gleaned from the household, the prerequisites being cleanliness and tight covering.

Maintenance

The clinical laboratory must be constantly scrutinized for the repair or replacement of faulty equipment, cleaning, oiling or readjustment of moving parts, replacement of chipped or scratched glassware, renewal of deteriorating reagents and the anticipation of expended materials. Whereas the supervision of this phase of laboratory function is rightfully the responsibility of the technician, the clinician should be alert to needs and freely and promptly provide, repair or replace any equipment and material that will contribute to efficiency, usefulness and a pleasant atmosphere in the laboratory.

Program of Service

It is inevitable that the more numerous and diversified the tests performed, the higher the overhead, and therefore the cost to the patient of the individual test. However, a reasonably extensive schedule will enhance the usefulness and prestige of the laboratory.

The number of different tests a laboratory may aspire to provide will depend entirely on the need. This is not to say that a good laboratory cannot develop a market for itself. Indeed, it can, and it should. Physicians who have had to do without may be slow to make use of additional facilities till they are familiarized with the purpose and assistance of the service afforded. For example, the hematocrit is still used far less in community offices and hospitals than merit-

Table 1. *Equipment for Use in Office Laboratory.**

Instruments	
Centrifuge (clinical)	Timing clock; mechanical counter.
Refrigerator	(Photoelectric colorimeter standardized for several tests)
Microscope (preferably binocular) with mech. stage	Urinometer (hydrometer type, with bulb)
Substage lamp with ground-glass & blue filter	Chapman water suction, with head for cleaning pipettes (blood & Wintrobe tubes)
Hemoglobinometer (Sahli)	Lens paper; filter paper.
Cedar oil (Shillaber's) for immersion	(Electrocardiograph)
Balsam or plastic mounting material	
Hemacytometer	

Glassware	
Test tubes, with brushes for cleaning	Hematology bottles
Centrifuge tubes, with brushes	Chemistry bottles
Graduated cylinders	Chemistry test tubes & stoppers
100 cc.	3 syringes, 5 cc.
50 cc.	
25 cc.	2 syringes, 10 cc.
10 cc.	1 syringe, 30 cc.
Funnels	
10-cm. size	5 hypodermic needles, No. 20
Beakers (graduated in cc. and ounces)	50-cc. burette with stand
1000 cc.	Sahli tubes & pipettes
500 cc.	
100 cc.	Microscope slides
50 cc.	Cover slips
(Water cells & tubes for photelometer)	Blood-count pipettes (Bard-Parker)
Medicine-dropper pipettes	Wintrobe tubes & pipettes
	Alcohol lamp (or Bunsen burner or both)
	Glass tubing
	Diluting pipettes, 1 to 10 cc.
	Bell jar for microscope
	Specimen bottles (blood & urine)

Miscellaneous		
Textbooks	Report forms	Card file
Facial tissues	Covered refuse can	Scotch tape
Containers for mailing, state, commercial, etc.		

*Adapted from Boardman,[3] with permission of the publisher.

ed by the simplicity and informativeness of the test. The same statement applies to many of the more recently introduced procedures.

To be reliable and economical, a test must be done frequently. Every test should be of sufficient clinical significance to justify its being done in a large percentage of cases that will yield normal values even though this presupposes an additional financial burden on the aggregate patient clientele.

Obviously, the needs and services of a doctor's office laboratory will be significantly less extensive than those of the laboratory in a group clinic. Indeed, the greater demand of a group of doctors on the laboratory (and ancillary services) contributes to the increased efficiency and reliability of such services. This may properly be considered an advantage of group practice.

Finally, the geographic location of the laboratory in relation to population and health centers will also dictate to some degree the scope of laboratory services. The office laboratory must be planned with the availability of laboratory services from other sources—for example, commercial, hospital, municipal and state laboratories—in mind if costly and needless reduplications are to be avoided.

Table 3 lists the more common laboratory examinations one might expect for a practitioner's office in populous areas and for the small group-practice laboratory or for a country doctor's office remote from commercial, hospital or state laboratories. The final column includes laboratory determinations offering real and reproducible clinical information in the hands of experts dealing frequently with the rarer clinical syndromes calling for such determinations. They are not for the offices of smaller groups and less specialized clinicians, being expensive, infrequently in demand and technically difficult.

TABLE 2. *Laboratory Reagents.**

HEMATOLOGY	
Wright's stain	
Buffer phosphate solution (pH 6.4) 0.07	
0.36% HCl (0.1 N). Dilute 1 cc. commercial HCl to 100 cc.	
Hayem's or Gower's solution (Gower's solution—6.25 gm. Na_2SO_4 & 16.67 gm. glacial acetic acid in 100 cc. water)	
Turck's solution	
Brilliant cresyl blue	
URINE	
Benedict's solution (qual.)	Nitrazine paper
Roberts' reagent	Sulkowitch reagent
Ammonia water	1.45% silver nitrate solution
Sodium nitroprusside crystals	Potassium chromate, 20%
Ammonium sulfate crystals	Ferric chloride, 10%
Clinitest	
Acetest or Acetone test (Denco)	
GENERAL	
Anticoagulants (see text)	
Distilled water	
Acetone	
Ether	
Alcohol, ethyl 95%—70% antiseptic	
Alcohol, methyl	
Alconox or other detergent cleanser	
H_2SO_4—K_2CrO_4 cleaning solution	
Xylol	
MISCELLANEOUS	
Gram's stain set	
Commercial test kits	
Hematest	
Wilkerson-Heftmann Screening Blood Sugar Kit	
Ictotest	
Potassium hydroxide, 10%	
Töpfer's reagent	
Phenolphthalein	
Pandy's solution	

*Adapted from Boardman,[3] with permission of the publisher.

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The office procedures need not include blood-typing and crossmatching, for instance, since transfusion is rarely indicated outside a hospital. Neither is it practical to include tests for which reliable public facilities are available and urgency is of relatively little importance, such as the serologic test for syphilis and smears and cultures to detect the tubercle bacillus.

Bacteriologic examination, like photoelectric colorimetry, is a highly technical exercise and should not be undertaken in most small laboratories.

Liver-function tests are legion. A few such procedures are relatively simple to perform. However, the multiple functions of the liver and its inter-relation with other metabolic systems and with the endocrines make evaluation of its performance vastly complex and still imperfectly understood. For this reason the simpler liver-function tests are of limited value by themselves. It is only with the information derived from a battery of tests, most of which are too complex for the purposes under discussion, that a differential diagnosis can be made in the most obscure hepatic disorders.

Recent Contributions

A recently developed test for urinary bilirubin has proved an additional aid in the bedside supervision of subclinical hepatitis, as in healing infectious hepatitis. This procedure provides one more measure of liver function on which the duration of bed rest may depend. Inexpensive, it is also more specific than either a shake test for bile in the urine or determination of the serum icteric index.

There is accumulating evidence that the excretion of calcium in the urine, as measured in an aliquot of twenty-four-hour specimen by use of Sulkowitch's reagent, is a practical and reliable measure of the osteolytic progression of bone metastases from advanced mammary cancer. Since therapy is symptomatic, depending on the arrest or progression of the disease as determined clinically, this affords practical information in office and bedside management.

Promise is shown in the field of bedside (or office) determination of blood and plasma electrolytes, notably chloride, bicarbonate and most recently potassium. A simple method of measuring blood nonprotein nitrogen has not yet been perfected. At present these procedures are for the better and more ambitious group laboratories to explore.

TECHNICS

Technics, like equipment, get rusty from disuse and deteriorate without refurbishing and periodic overhauling. As with stock reagents, stock procedures need

freshening and replacement. The essence of good technic, then, is a constant awareness of the fallibility of routinization, and the unceasing objective inquiry into the purpose, procedure and pitfalls of each performance of every examination. The doctor will do well to scrutinize the laboratory data critically and to question any discrepancy between it and clinical findings, not for the purpose of placing blame but only to correct errors whenever found.

The validity of the individual test may be tried against results in other laboratories with duplicate samples of the same blood or by the submission of both duplicates under different names to the laboratory without the technician's knowledge. This is an accepted method of checking technics and should be discussed in principle with the technician.

Several features of office laboratory procedure differ materially from that found in hospitals. In the office laboratory the convenient time of collecting specimens is during or shortly before the patient's visit to the attending physician. Hence, the blood may show a leukocytosis, lipemia or elevation of sugar concentration after meals. An "early morning specimen" of urine may be eight hours old on delivery, and unsuitable for microscopical study.

Specimens taken during house calls may be several hours old, shaken up or exposed to excesses of heat or cold, unless attention is paid to these details.

TABLE 3. *Tests for Use in the Office Laboratory.**

SPECIMEN	TESTS MADE BY PHYSICIAN PRACTICING ALONE	SMALL GROUP OR REMOTE LABORATORY OF COUNTRY PRACTITIONER	TESTS NOT REQUIRED OF OFFICE LABORATORY
Urine	Routine examination (appearance, pH, specific gravity, glucose, acetone, albumin, microscopical) Bile 24-hr. quantitative sugar	Diacetic acid, Phenolsulfonephthalein test Quantitative albumin Bence-Jones protein	Ketosteroids Hormones Pregnancy Urobilinogen
	Mosenthal concentration & dilution Chloride; calcium (24-hr. qualitative).		
	Bilirubin		
Blood	Routine (hemoglobin, hematocrit, white-cell count, differential) Erythrocyte sedimentation rate Blood sugar (screening) Bleeding & clotting times Red-cell count Mean corpuscular hemoglobin concentration	Chloride & bicarbonates Reticulocytes Fungi Glucose tolerance test Blood parasites Prothrombin time	Electrolyte partition gases Serum proteins Vitamins Flame photometry Liver-function tests Spectrophotometry Microanalysis L. E. test Protein-bound iodine & I^{131} Thorn's eosinophil count Photoelectric-cell use Fragility & sickling Typing & crossmatching Serologic test for syphilis Nonprotein nitrogen Mean corpuscular volume Mean corpuscular hemoglobin
	Color index		
Stool	Inspection for appearance, blood & pus, pinworms	Ova & parasites	Fats, chemical analyses & others
Stomach	—	Gastric analysis Duodenal drainage	Concentration of acid-fast bacilli or malignant cells
Spinal fluid	Inspection for appearance, cells, protein	Glucose Wright or Gram stain	Serology, colloidal gold, quantitative, culture
Sputum	Appearance, quantity, blood	Methylene blue, gram, acid-fast and Wright stains	Concentration of acid-fast bacilli Fungi
Bacteriologic culture	Not usually included in small laboratory	Cultures for *Escherichia coli* and beta-hemolytic streptococci; blood-agar plates & mediums for growth & transportation; gram, Loeffler's & acid-fast stains.	Culture, identification & determinations of sensitivity to various antibiotics
Miscellaneous	Venous pressure, vital capacity, circulation time	Electrocardiogram Bromsulfalein Icteric index, etc.	Basal metabolic rate X-ray examination Papanicolaou interpretation
	Fluoroscopy Papanicolaou collection & fixation		

*Based on Boardman.[3]

Every laboratory must be alert to the importance of meticulous cleanliness, quantitative precision, appropriate sterilization and drying of needles, syringes and containers. Time spent by the physician in the instruction of himself or of the technician in the niceties of venipuncture technic, sharpening and cleansing of needles and preparation and aftercare of the patient's punctured vein will make the experience a decreasingly traumatic one for all concerned.

Community Facilities

As already intimated the office laboratory will prove most useful as a complementary adjunct to existing laboratory services available to any physician establishing a practice in a new community. To endeavor to supplant or compete with reliable and prompt laboratory services already adequately providing a community need is not only extravagant but also a disservice to all concerned—laboratories, patients and physicians. The community-hospital laboratory in particular needs the support of outpatient referrals from the members of the staff. This support should be given gladly whenever feasible, for the hospital is the focal point of one's practice.

One's own clinicopathological excursions, then, will depend to no little extent on the availability, reliability and scope of community laboratories, whether they are in the local hospital or in commercial, municipal or state and national laboratories. Availability, of course, implies the relative factors of distance, public conveyance, frequency of use of a specific procedure, speed or urgency of completion (from the decision to require it to receipt of the report) and the stability of the material.

Although it is within the province of the laboratory personnel to be familiar with and responsible for all these data, the physician himself will wisely visit not only the clinical laboratory of the community hospital but also any commercial laboratory that he intends to patronize. For whereas the performance of some laboratories meets high standards, most of them need close scrutiny, particularly in the matter of uncritical acceptance of specimens without regard to conditions of delivery. Many commercial laboratories fall below the minimum standards of technic and reliability, a fact readily recognized from a visit.

There are, unfortunately, laboratories whose work is not only inaccurate but also irresponsible. These are best shunned entirely.

Although one may well assume the validity of most municipal and state clinical laboratories, it is well to appraise the work done and the correctness of the reports received. A visit may establish a rapport and mutual respect that a decade of correspondence might not achieve.

The United States Public Health Service publishes a yearly *Directory of State and Territorial Health Authorities*[4] for those interested in a national view in anticipation of selecting a region for settlement. State authorities will provide detailed information of district, county and municipal facilities.

Much of the foregoing seems obvious enough, but it is a deplorable fact that many community-hospital laboratories and a majority of practicing physicians either are unfamiliar with the public services available to them or ignore them for any of a number of reasons. The establishment of a familiar liaison with such facilities early in one's practice, while time hangs heavy, will lead to a habit pattern useful throughout one's professional lifetime.

Personnel

The successful practitioner soon finds that his clinical responsibilities do not leave him the time needed for the corresponding laboratory studies. With the introduction either of a factotum secretary-receptionist-bookkeeper-laboratory technician or of several ancillary personnel his problems are compounded. In either event a personnel problem exists.

Implicit in much that has gone before has been a concern for personnel morale. This aspect of operation, in fact, represents the major complication of an office laboratory. In a facility where only the simpler tests are performed a close clinical liaison affords the best stimulus to the technician's continued interest in and appreciation of the significance of the work. Repeated reminders of the contribution to diagnosis and treatment made by laboratory information and discussion of the pathological physiology causing abnormal laboratory findings will demonstrate appreciation too often unexpressed. Prompt, frank and objective re-evaluation of tests affording discrepancies either incongruous or recurring with unlikely frequency will serve to convince the technician that laboratory reports are more than "window dressing" or sources of office income.

It is inconsistent to expect order and cleanliness of the laboratory and consequent meticulousness and accuracy of performance if the physician does not give adequate attention to and funds for its equipment and furnishing.

It is therefore incumbent on him to be thoroughly familiar with the technic, the sources of correctible error, the reproducibility and the normal range and significant deviations of all tests performed in his office laboratory. The continued use, objective re-evaluation of accuracy and reassessment of the current or alternative technics of performance should be assured. The doctor should also be familiar with the new technics or new tests appropriate for such a laboratory as they appear in the literature and should discuss, practice and carefully appraise new procedures with the technician, checking by multiple samples and comparison with the findings of other experienced laboratories. Finally, he should make available to the technician the current literature in the textbooks of clinical pathology, in the *American Journal of Medical Technology* and perhaps the *American Journal of*

Clinical Pathology, or even in the *Journal of Laboratory and Clinical Medicine* and the *Journal of Clinical Investigation*. The first of these journals should be considered basic to an office laboratory. The others can be scanned briefly in a medical library at intervals, and procedures and discussions suitable for office use appropriated.

The personnel problem in a group clinic affords one more hazard: that of the relations between the laboratory and the clinicians. This is specifically a matter of clearly defining authority and responsibility. Since the clinicians will have much to do with the preparing of the patient and the collection and transportation of samples, they must be kept constantly aware of the importance of discharging this responsibility. Similarly, the laboratory must be represented by one familiar with clinical implications.

A group-clinic laboratory then should be under the direct administrative and professional supervision of a physician who in turn is responsible to the staff for the maintenance of high standards of performance.

Acceptance by the Patient

The introduction of laboratory studies into the family doctor's role even now meets with resistance from the patient in a large percentage of the population. This is a reflection more on medical socioeconomics than on medical education. If the physician sends his patients to a commercial or hospital laboratory for studies the patient will resent the added expense more than he will doubt the doctor's clinical acumen, but if the diagnostic studies are done in the doctor's office and therefore the fee to the office is increased, the doctor will promptly be suspected of "overcharging." Yet, in this day of wider knowledge and definitive therapy, it is inexcusable to attend any but the briefest and most trivial of ills without benefit of the supportive information of basic laboratory studies. That symptomatic therapy continues to be the rule rather than the exception is attributable in part to economic pressures and in part to professional lethargy, for an explanation to the patient takes time and is not always satisfactory. In many communities the performance of laboratory studies will be an innovation, and patients are sometimes even slower than doctors to accept change.

Nevertheless, experience has shown that this service is ultimately not only accepted but appreciated and even boasted of by patients who were skeptical and resistant at first.

Financing and Administration

A laboratory should not be a source of significant profit. It should pay its way, including a fair recompense for the physician's time, effort and experience in supervision and administration. The more versatile the service, the more costly the operation, and the higher the rates to the patient. Any scale of prices will have to be adjusted accordingly, and individual charges will necessarily be tailored to the patient's resources and his total medical expenses. In any event the laboratory fees should be clearly distinguished in the patient's mind from professional fees, and the cost indicated in a general way before the tests are done.

Much of the administrative responsibility has already been outlined. Here it is necessary only to reemphasize the importance of a clear understanding of the respective spheres of responsibility between technician and physician and, in medical groups, between the clinician in charge and the rest of the medical staff.

It is well to emphasize here the obvious but often neglected obligation to record all data, both on the patient's record and in the laboratory file.

Summary and Conclusions

The addition of basic laboratory services to the professional services of a doctor, although conducive to significantly superior medical practice, introduces a number of ponderable obstacles and responsibilities. Some of these are briefly discussed. Space and equipment requirements are outlined.

It is emphasized that laboratory data are indispensable to the practice of modern medicine, with its clearer understanding of physiology and pathology and its wealth of definitive therapy. It is recommended that the operations of an office laboratory, for the physician practicing alone or for a medical group, be restricted to a minimum, serving only to complement the services of the larger, established clinical laboratories of hospitals, community and state. To facilitate the full utilization of these, however, is a function of the office laboratory.

The essential factor of a vital and effective laboratory is a close liaison between technician and physician, with reciprocal discussion and criticism of procedure, technic, sources of error and innovations.

Since personnel morale is the major stumbling block to competent office laboratory services, attention is called to the fine line between sufficient repetition to assure sustained perfection of technic and a schedule wide enough to hold the technician's interest. The problem of acceptance by the patient is evaluated, and the responsibility of the physician to educate his patients to a better type of medical care is shown to be justly rewarded.

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MEDICAL PROGRESS

ANESTHESIOLOGY*

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THE development of anesthesiology since World War II has been characterized by several distinct paths of clinical and scientific activity. Efforts have been made to provide better clinical anesthetic care for more patients by the strengthening of residency training programs. Aid has been given the surgeon in his desire to extend operative treatment to previously inaccessible organs, such as the heart, and to patients whose risk for operation was considered prohibitive two decades ago. However, these twin activities depend on the acquisition of basic knowledge concerning physiologic derangements in the anesthetized state regardless of the specific anesthetic agent employed. This activity of gaining better understanding of body function has dominated progress in anesthesiology in the postwar period to a significant degree. Even the constant study of newer anesthetic agents and methods has been fitted to this larger scheme of things in that work with newer compounds has been directed toward chemical properties that may cause fewer disturbances in normal function than the established agents.

The purpose of this discussion is, therefore, to examine and summarize some of the studies that were designed to enlarge knowledge of physiologic changes induced by the administration of anesthesia.

Acid-Base Balance and Problems of Ventilation

Acidosis during anesthesia was observed in the 1920's. A decrease in the serum bicarbonate and pH of the blood and an increase in phosphate and lactate in the plasma were demonstrated during ether anesthesia.[1,2] Recently, the problem of acid-base balance during anesthesia has again been brought into focus. With the aid of improvements in analytic technics, the development of acidosis during general anesthesia was correlated with the factors inducing diminished pulmonary ventilation. The effect of acidosis on the circulation was also studied by some groups.

During ether anesthesia, Holaday and his co-workers[3] corroborated earlier work by reporting a progressive decrease in the blood pH. If the surgical procedures do not involve an open thorax the available buffer base of the plasma decreases at a more or less constant rate as the anesthesia proceeds, even though the carbon dioxide tension of the arterial blood is not materially changed. In a group of 16 patients the average maximal change of buffer base during ether anesthesia was a decrease of 7 milliequiv. per liter. The arterial-blood pH and buffer-base values gradually returned to normal after the termination of anesthesia. However, Beecher et al.[4] observed an insignificant increase in fixed acid of 2.1 milliequiv. per liter in adult patients during ether anesthesia. In a later report this group of workers[5] described moderate to severe metabolic acidosis during ether anesthesia in children and occasionally in adults. They found that it was associated with a rise in serum lactate. They suggested that this metabolic acidosis was probably related to overactivity of the sympathetic nervous system, which leads to overproduction of lactate. The decreased utilization of lactate in certain conditions probably also was a factor. Foldes and his colleagues[6] observed an increase of inorganic phosphate in the serum during ether and cyclopropane anesthesia, confirming the earlier work of Stehle and Bourne and Ronzoni.

Cyclopropane is a powerful respiratory depressant. Holaday et al.[3,7] reported that respiratory acidosis occurred frequently, even with assisted respiration, during anesthesia with cyclopropane. This respiratory acidosis was accompanied by a parallel metabolic acidosis. With adequate ventilation, both forms of acidosis were prevented and could be reversed if they had developed. This causal relation between respiratory and metabolic acidosis was also found to be true with other anesthetic agents. The mechanism for the development of metabolic acidosis consequent to respiratory acidosis is not clear at present although this phenomenon has been known since 1932.[8]

The development of acidosis is even more dramatic during anesthesia for intrathoracic operations. The patient's position and the open thorax, in addition to the effect of anesthetic agents, impede ventilation. Reports from several groups of investigators[3,9-16] indicate that the reduction in blood pH under such conditions may be of considerable magnitude; pH values lower than 7.20 were a common finding for patients undergoing lung resections, and in extreme cases it reached 6.82. The mechanism for the development of such a marked acidosis was sought. Beecher and his co-workers[14] concluded that the lateral operative position may be responsible since they found a less marked change in pH values in patients undergoing intrathoracic procedures in the prone position. However, Etsten[15] demonstrated that acidosis

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developed regardless of the patient's position and that it was associated with the hypoventilation consequent to surgical pneumothorax and deep anesthesia. The duration of anesthesia played no part. Stead, Martin and Jensen[16] demonstrated an excellent correlation between the pH changes and alveolar ventilation in contrast to total ventilation during intrapleural surgery. Maintenance of total ventilation at control levels did not necessarily prevent the development of respiratory acidosis during pulmonary resection. In 1 patient, when the total ventilation was kept above normal, with alveolar ventilation at control levels, the pH and carbon dioxide tension were not altered. However, Carpenter et al.[17] found that, in patients with an intact thorax, the arterial pH and carbon dioxide tension were a close function of the total ventilation. A minute volume of 6 liters was found to be adequate for maintaining a normal arterial carbon dioxide tension in anesthetized adults under these conditions.

There are no reliable clinical signs accompanying acidosis during anesthesia to inform the anesthesiologist that significant physiologic alterations are taking place.[5,12,18] The pulse rate and arterial pressure may not change, and cyanosis is noticeably absent. With the usual high concentrations of oxygen in the anesthetic mixture, the oxygen saturation was usually well maintained in the cases studied. Some devices have been developed to measure the earbon dioxide content of the expired air[18,19] or to measure the ventilation volume continuously during anesthesia.[20] However, these devices are not available as yet for ordinary clinical use.

The question of the clinical importance of respiratory acidosis during anesthesia has been raised. Is this acidosis responsible for some of the serious postoperative complications and anesthetic deaths? Observations in man and in dogs provide strong evidence that acidosis during anesthesia can indeed be held responsible for serious complications during and after anesthesia. Dripps[21] and Buckley and his associates[22] have shown that severe hypotension may be the consequence of postanesthetic recovery from respiratory acidosis. However, in these studies, if the alveolar carbon dioxide content was maintained at normal levels by assisted respiration, the majority of patients showed no decrease in blood pressure after anesthesia.

It is a classic concept in physiology that the isolated perfused heart cannot function if the pH value falls below 7.0. Gertler[23] observed that the dog heart in situ can tolerate a pH of 6.25. Altschule and Sulzbach[24] gave 5 per cent carbon dioxide in 95 per cent oxygen to psychotic patients with morphine as premedication. With the arterial blood pH lowered to 6.90 they noticed electrocardiographic changes indicating myocardial injury. Nodal rhythm occurred in some cases. Whitehead and his co-workers,[25,26] in studies of diffusion respiration in dogs, found that the arterial blood pH reached the lowest value of 6.7 forty-five minutes after the start of diffusion respiration. Electrocardiograms showed a progressive rise in the amplitude of R and T waves and premature ventricular contractions. Miller et al.[27-29] allowed dogs to breathe an atmosphere of high carbon dioxide concentration. They also observed electrocardiographic alterations: increased amplitude of T waves, occasional ectopic beats and depression of the ST segment. On sudden withdrawal of the carbon dioxide a wide variety of changes occurred, indicating heart block and increased myocardial irritability. Seventy to eighty per cent of the dogs developed ventricular fibrillation and died. The authors[29] concluded from several studies that "A patient after a prolonged and severe siege of respiratory acidosis, hovers on the brink of disaster, if suddenly ventilated with a mixture low in carbon dioxide concentration." They stressed the need for sustained and competent supplementation for respiration throughout the period of anesthesia, which is mandatory and may be life saving.

The irritability of the heart and its response to direct or reflex vagal stimulation are also increased during respiratory acidosis. Sloan,[30] Young et al.[31] and Campbell, Haddy and Brown[32-34] demonstrated during respiratory acidosis that stimulation of the vagus nerve of the dog, either reflexly or directly, caused a greater fall in blood pressure and a longer duration of asystole when the animals were compared with nonacidotic dogs. The same authors[32] showed that the reverse is true with alkalosis. They suggested that the activity of cholinesterase (optimal at pH of 7.5 to 8.5) may be responsible for the difference of responses of the heart. It is not unreasonable to conclude from these findings that patients are more vulnerable to reflex vagal stimulation during anesthesia if they have acidosis. Deaths from the "vagovagal" reflexes on endotracheal intubation or suction might be explained on this basis.

The importance of providing effective alveolar ventilation for patients during general anesthesia is clearly established. Adequate ventilation can be accomplished by rhythmic manual pressure on the rebreathing bag. This requires undivided attention and effort by the anesthesiologist. An alternative method is the use of mechanical ventilators or respirators to ensure efficient and uninterrupted gas exchange. During mechanical ventilation it is essential that the maximum positive pressure be moderate and its duration not too prolonged to avoid interference with the venous return and the cardiac output. Cournand et al.[35] demonstrated in conscious subjects that the cardiac output is reduced 14.3 per cent if the peak mask pressure is 14.2 mm. of mercury with a mean mask pressure of 7 mm. of mercury and the positive pressure phase is prolonged. Such an effect on the circulation may not be important in healthy patients, but "in patients who do not have a normal circulatory reserve, a small amount of intrapulmonary pressure may have serious consequences."[36] Maloney and his

associates[37] also emphasized the increased significance of these deleterious effects in patients with a decompensated circulation.

The introduction of a negative phase during intermittent pressure ventilation has been advocated by some. Brecher[38] demonstrated in dogs that the application of intermittent positive-negative pressure ventilation increases the venous return significantly over that existing during intermittent positive-atmospheric pressure ventilation. However, Greene[39] showed that in dogs with a tendency to pulmonary edema (pretreated with ANTU) the positive-negative ventilation aggravates this condition. At present much work has to be done before the positive-negative ventilation can be evaluated adequately and applied clinically.

It is therefore abundantly clear that efficient ventilation is necessary to prevent and treat respiratory acidosis during general anesthesia to avoid the metabolic and circulatory sequelae associated with acidosis. All the factors desirable in obtaining adequate ventilation without the impact of pressure breathing on the circulation are not completely delineated and are in the process of further investigation.

Renal Function and Hemodynamic Changes During General Anesthesia

The kidney plays an important role in the circulatory and metabolic adjustments in health and disease. It has been known that a variety of conditions, such as violent exercise, venous congestion, anoxia and stress of any kind, can alter renal function to a great extent. It has also been shown that general anesthesia depresses the formation of urine and may be associated with salt retention in the postoperative period. Recently, extensive studies on renal function during anesthesia were carried out to examine more precisely the nature of these alterations.

Earlier investigations by Coller and his associates[40] in man showed that there was no significant change in renal function after ether or cyclopropane anesthesia. Craig et al.[41] found in dogs that light cyclopropane and ether anesthesia did not alter renal function. During deep anesthesia, however, the renal blood flow, glomerular filtration rate and tubular activity were reduced approximately 50 per cent. The studies of Habif and his co-workers,[42] Burnett and his associates[43] and others[44-47] in human patients during general anesthesia yielded different results from those of Coller et al.[40] Habif and his group observed profound depression of various renal functions during ether, cyclopropane and thiopental nitrous oxide anesthesia, and also significant alteration of renal function after administration of narcotic premedicant drugs.

According to Habif and his co-workers[42] the administration of meperidine and morphine in therapeutic doses was followed by a fall of glomerular filtration rate (21 to 45 per cent) and effective renal plasma flow (24 to 50 per cent). The filtration fraction rose slightly, and this was interpreted as evidence of intrarenal vasoconstriction. The urine flow also decreased, particularly during a water diuresis. The decrease in urine flow was associated with increased urinary concentration of sodium, potassium and chloride, but the total electrolyte excretion diminished. The tubular reabsorption of water, sodium and chloride in proportion to filtration was increased. With general anesthesia there was a striking reduction of the glomerular filtration rate, the effective renal plasma flow and the output of water and electrolytes, immediately or shortly after the induction of anesthesia. The fall in filtration was usually less marked than that in effective renal plasma flow, so that the filtration fraction rose. The extraction of para-aminohippuric acid was not changed. Since these alterations were associated with either no change or a slight rise in the arterial pressure, a marked intrarenal vasoconstriction must have occurred, presumably affecting both afferent and efferent arterioles. The urine flow fell to a very low level, and in a few cases it ceased altogether. The output of water and electrolytes decreased more than the filtration, indicating a relative augmentation of tubular reabsorption. On termination of the anesthesia all values returned to, or almost to, preanesthetic levels. The changes with cyclopropane anesthesia were more profound than those with ether. These changes in renal hemodynamics and function with general anesthesia were in keeping with the observations of Burnett et al.,[43] Lee and his co-workers,[44,45] Moyer[46] and Bachman.[47] They are nonspecific so far as the anesthetic agent is concerned and seem to be associated with the state of general anesthesia. Operative trauma does not usually aggravate these changes in the absence of shock and hemorrhage.

The mechanism of the renal vasoconstriction was sought, and the results of studies in laboratory animals and in man indicate that renal nerves do not participate in the regulation of renal hemodynamics. Berne and Levy[48] observed in dogs that when the cardiac output was acutely reduced by pulmonary arterial constriction, the changes in renal blood flow, glomerular filtration rate and sodium excretion were the same in innervated and denervated kidneys. Papper[49] stated that high spinal anesthesia did not alter the renal responses to general anesthesia provided that no change in blood pressure had occurred. Miles and his co-workers[50] failed to observe any significant changes in renal hemodynamics and renal function during anesthesia after ganglionic block with methonium compounds. On the other hand the intravenous infusion of epinephrine and nor-epinephrine resulted in changes in renal function strikingly similar to those caused by anesthesia.[51,52] The available evidence does not warrant a definite conclusion, but it is possible that the renal responses to general anesthesia are humoral in origin and the result of the release of adrenal medullary hormones.

Several studies have also demonstrated vasoconstriction in the splanchnic bed during general anesthesia. Habif et al.,[42] using the bromsulfalein method,[53] observed during cyclopropane and thiopental anesthesia a decrease in the estimated hepatic blood flow with an increase in the arterial-hepatic venous oxygen difference. There was little or no alteration in oxygen consumption. Shackman, Graber and Melrose,[54] with a similar technic, showed during thiopental cyclopropane anesthesia that a decrease in estimated hepatic blood flow of 30 per cent occurred regardless of arterial pressure changes and thus represented an increase in the splanchnic vascular resistance. Contrary to the finding of Habif et al. they concluded that the oxygen consumption of the liver and the splanchnic circulation was reduced 34 per cent. (Total oxygen consumption by the body is decreased 20 per cent during anesthesia.[55])

Since the splanchnic and renal vascular beds constitute a major part of the total peripheral circulation, the profound alteration of vascular resistance and blood flow in these areas is of great importance to total circulatory homeostasis during anesthesia. Other peripheral beds have been studied. Wechsler, Dripps and Kety[56] reported that the cerebral blood flow was not changed during thiopental anesthesia. Shackman et al.,[57-59] using the direct Fick method for measuring cardiac output and plethysmography for skin and muscle blood flow, demonstrated that there was a profound vasodilatation in the skin and muscle and a slight fall in cardiac output early in the course of anesthesia. The arterial pressure was not changed. When anesthesia was deep or prolonged the cardiac output was reduced further, and the skin and muscle blood flow fell. The total peripheral resistance was increased in 72 per cent of the cases studied. Lee and his associates[44] observed similar changes and, in addition, found that the intrathoracic blood volume was not significantly altered.

Therefore, it is clear that even well conducted general anesthesia causes a severe derangement of circulatory dynamics. In the early phases of prolonged anesthesia the splanchnic and renal vasoconstriction persist whereas the peripheral blood flow decreases. The arterial pressure is relatively unaltered if anesthesia is not too deep, and cardiac output falls in almost all cases. The basic, underlying physiologic mechanism certainly is not simple or easy to ascertain.

A clue is provided by the fact that the circulatory changes that have been observed are associated with all forms of general anesthesia. There are inconsequential differences among the various anesthetic agents, suggesting that some basic mechanism governs the body's circulatory responses to general anesthesia.

Relaxants

Since the introduction of curare to clinical anesthesia by Griffith and Johnson[60] in 1942 the use of muscular relaxants has greatly increased. There has been much discussion and some controversy concerning the value and safety of muscle relaxants in clinical anesthesia. We are firmly convinced that these agents are of considerable clinical value and believe that a thorough familiarity with their physiologic effects is the best means for proper selection and safe usage. This is not to deny the dangers of the relaxants, but to insist that, like other potent drugs, they be employed by qualified people in a skillful manner.

In recent years a number of new synthetic relaxants have been prepared and introduced to clinical use. The question of which drug is most appropriate to a given clinical situation is thereby raised.

As Paton[61] has pointed out, as far as the neuromuscular blocking action of an agent is concerned, there are not only species differences but also differences in the sensitivity of various groups of muscles. Evaluation of a new relaxant for its clinical efficacy and safety must ultimately be carried out on human subjects. To this end many excellent studies have been made, contributing materially to the appreciation of the action of each drug under a variety of clinical conditions.

All relaxants can be classified in two groups according to the mechanisms through which neuromuscular block is accomplished. One group of agents blocks neuromuscular transmission by interfering with normal activity of acetylcholine released at the motor nerve endings. These agents stabilize the motor end plate and prevent depolarization. The end plate resting potential is not changed, and neuromuscular blockade can be antagonized with anticholinesterase and "depolarizing agents." In denervated muscles they have little or no effect on the response from direct muscle stimulation; d-tubocurarine, dimethyl d-tubocurarine, Flaxedil and Mytolon belong to this group. The other group of agents affect neuromuscular transmission by depolarizing the motor end plate so that it becomes refractory to motor impulses. During the early phase of the depolarization the excitability of the end plate is actually increased before it passes into the state of refractoriness. The paralysis is usually preceded by a period of muscle fasciculation. Anticholinesterases have little or no potentiating effect on their action, and in laboratory animals appropriate concentrations of d-tubocurarine or other "depolarization-blocking" agents have antagonistic actions. Two relaxants with these characteristic actions are decamethonium and its analogue, Ro3-6386. Succinylcholine is a depolarizing agent, but its action is markedly potentiated by anticholinesterases.

However, such a classification of relaxants only indicates the main pharmacologic activity of each agent at the neuromuscular junction. Indeed, with paralyzing or higher concentrations it was demonstrated that many drugs have multiple sites of action. In the following paragraphs the pharmacology of each of the relaxants and their clinical applications are discussed.

d-Tubocurarine

Marsh,[62] studying the fate of d-tubocurarine in the body, observed that the injected d-tubocurarine was distributed universally, and no increased concentration at the neuromuscular junction could be demonstrated. In man the initial plasma concentration reached the theoretical maximum immediately and promptly began to diminish. Within less than ten minutes the plasma level fell to two thirds of the original level. Thirty per cent of the administered dose was excreted in the urine. Marsh concluded that the duration of the paralytic action of d-tubocurarine after a single injection was related to the rapid redistribution and not to the rate of metabolism or rate of excretion. Only with repeated dosage, after the saturation of all depots, did the paralytic action become prolonged and dependent on the rate of metabolism and excretion. Pittinger, Morris and Cullen[63] found that the resumption of intercostal muscular activity could not be correlated precisely with plasma concentration even though plasma levels decreased rapidly. However, if the plasma concentration was higher than 3 microgm. per cubic centimeter the intercostal muscles remained paralyzed.

The histamine-like activity of d-tubocurarine was demonstrated by appropriate skin responses to an intradermal injection of the drug. The bronchoconstrictor effect of injected d-tubocurarine was recorded in anesthetized man by Landmesser et al.,[64] but it occurred much less regularly than in laboratory animals. Guyton and Reeder[65] pointed out that the paralysis of parasympathetic functions in the dog required one and a half times as much curare as was necessary for skeletal-muscle paralysis; paralysis of sympathetic functions was obtained with five to ten times the dose that effected skeletal-muscle paralysis. The translation of these findings to man is not necessarily certain.

The question of the central action of d-tubocurarine remains unsettled. McCawley[66] observed in unanesthetized dogs that curare induced central-nervous-system stimulation, manifested by convulsions and spike discharges in the electroencephalogram. At a markedly elevated dosage curare caused an irreversible depression of the central nervous system, demonstrated by the depression of electroencephalographic activity and internuncial transmission through the spinal cord. However, the depression could have been secondary to the depressed circulation and not to the direct action of the drug. Ellis, Morgan and de Beer[67] also studied the central depressant action of d-tubocurarine, decamethonium and succinylcholine. They observed that the animal remained apneic, and spontaneous phrenic-nerve action potential was absent during recovery from a large dose of these agents, at a time when the diaphragm responded to electric stimulation of the phrenic nerve. They concluded that the protracted respiratory arrest after restoration of neuromuscular transmission indicated a depressant action of these agents on either the respiratory center or other nervous elements. But such a conclusion is open to question, for the absence of rhythmic discharge of the respiratory center could be the result of hyperventilation and hypocapnea, since artificial ventilation was maintained throughout the period of paralysis. Further studies with regulated ventilation are necessary before any definite conclusion can be drawn.

The placental transmission of d-tubocurarine was studied in laboratory animals and in man. Buller and Young[68] showed that there was no difference between the sensitivity of adults and that of late-term fetuses to d-tubocurarine in the rabbit. Intravenously administered d-tubocurarine did not cross the placenta in sufficient quantity to cause respiratory arrest in the fetus. On the other hand Pittinger and Morris,[69] by injecting large doses (45-60 mg.) of d-tubocurarine into the uterine artery in dogs, demonstrated placental transmission of the drug in sufficient quantities (1.3 to 2.5 microgm. per cubic centimeter in fetal plasma) to cause fetal respiratory paralysis. However, this finding does not appear to have clinical significance, since it is unlikely that this concentration of d-tubocurarine will be present in the maternal blood stream under clinical conditions. Cohen and his co-workers[70] studied the placental transmission of d-tubocurarine in man. In a series of 124 cesarian sections d-tubocurarine was used in the large dose range of 18 to 42 mg. The maternal plasma concentration of d-tubocurarine at birth averaged 14.1 microgm. per cubic centimeter, and no d-tubocurarine was demonstrated in the fetal blood. Therefore, it is probable that with reasonable clinical paralyzing doses d-tubocurarine does not cross the placenta in sufficient quantity to endanger the newborn.

(To be continued)

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MEDICAL INTELLIGENCE

USE OF CHLORPROMAZINE IN THE TREATMENT OF NAUSEA AND VOMITING OF UREMIA*

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NAUSEA and vomiting, which are common complications of uremia, may cause only mild distress or may be of such severity as to create a distinct hazard to the patient. Nausea interferes with proper food intake, and frequently an inadequate, unbalanced diet results. Furthermore, the associated mental and emotional distress may prove most unpleasant to the patient, seriously exhausting him and undermining his ability to resist the disease. Persistent vomiting is dangerous and can lead to serious consequences if not properly and adequately controlled. It not only is capable of upsetting electrolyte balance, creating dehydration and exhausting the patient. but also carries with it the ever-present possibility of aspirating vomitus into the lungs or precipitating a gastric hemorrhage.

Patients with uremia who have severe nausea and vomiting are most difficult to regulate properly. They have rapid fluctuations in electrolytes and, for the most part, require intravenous medication, which further complicates their therapy. Every physician who has treated many of these patients realizes that if nausea and vomiting could be controlled, the management would be much more simple and satisfactory.

The exact cause of the nausea and vomiting in uremia is not known. It is thought by some to be retained toxic metabolites that act on the emetic areas in the brain. Others consider that the uremia causes gastrointestinal irritation, which precipitates nausea and vomiting. Since ulceration of the mucosa of the stomach or bowel is observed in many cases gastrointestinal irritation undoubtedly occurs. It is reasonable to suppose that either or both factors may operate in any given case.[1] Certainly, nausea or vomiting or both occur in a high percentage of these patients and are not effectively relieved until the uremia

TABLE 1. *Effects of Chlorpromazine on Hematocrit and Electrolytes in Various Diseases.*

PATIENT	HOSPITAL NO.	DIAGNOSIS	HEMATOCRIT	BLOOD UREA NITROGEN	CARBON DIOXIDE	SODIUM	POTASSIUM	CHLORIDE
			%	*mg./100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
N.M.	8F789	Malignant hypertension, glomerulonephritis (chronic) & azotemia	23 24	80 126	16.9 17.8	134 124	3.5 5.2	103 88
J.P.	2A915	Chronic glomerulonephritis	20 30	153 194	16.0 12.7	126 137	4.6 3.9	95 109
W.E.	7F686	Chronic nephritis	26 35	80 73	20.7 26.3	— —	— —	110 105
S.F.	7F51	Chronic pyelonephritis	27	89	18.8	137	4.7	105
J.M.	0F225	Malignant hypertension & uremia	32 32 34	74 80 100	24.1 26.3 21.6	135 131 122	5.3 3.7 4.1	108 93 89
R.K.	6B83	Diffuse collagen disease; subacute nephritis.	45 48	125 100	22.7 23.7	133 137	6.4 3.5	100 109
M.A.	6B66	Chronic pyelonephritis	24 20	180 195	11.2 10.0	126 109	3.3 6.6	92 81
E.S.	7F311	Disseminated lupus erythematosus	36 —	85 90	19.4 26.9	138 131	6.5 5.8	108 110
D.H.	7F607	Bichloride of mercury poisoning, with oliguria	34 27	144 132	23.0 —	138 132	6.0 5.0	86 —
A.P.	7F29	Glomerulonephritis	31 23	180 232	15.4 12.2	126 124	5.5 7.3	97 98
E.G.	7F395	Lower-nephron nephrosis	18 20	190 187	14.3 19.0	137 147	4.1 4.8	114 104
W.O.	0H2	Kimmelstiel-Wilson disease	31.8 40	56 66	— —	— —	— —	— —
H.R.	0H1	—	33 33	35 50	24.0 —	— —	— —	— —
C.F.	7F935	Chronic nephritis	33 22	247 270	12.9 15.5	127 126	3.2 4.5	96 96

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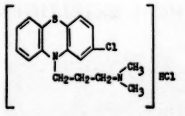
is corrected, either by recovery from the initiating lesion or by dialysis with the artificial kidney. Occasionally, they do not subside readily even after the chemical constituents of the body have returned to normal. Some of these patients may still have considerable gastrointestinal irritation that, in the presence of an already irritable vomiting center, is sufficient to prolong nausea and vomiting.

We became interested in the problem when a new chemical agent that had been shown effective in animal experiments in blocking the emetic effect of apomorphine[2-4] was made available to us. The drug was first cautiously studied in patients with terminal cancer associated with nausea or vomiting, and found to be capable of suppressing the symptoms in a high percentage of cases.[5] It was without serious demonstrable toxic effects and gave such good results that we decided to see what it would do for the nausea and vomiting of severe uremia.

Chlorpromazine,* known experimentally as SKF No. 2601-A (4560 R. P. in France and Largactil in Canada and elsewhere abroad), was synthesized in the Rhône–Poulenc Special Research Laboratories in France. It is a chlorinated phenothiazine (10-[-dimethylaminopropyl]-2-chlorophenothiazine) having the following formula:



*Kindly supplied by Smith, Kline and French Laboratories, Philadelphia, as Thorazine.

Material and Methods

Patients whose vomiting had persisted for three or four days in spite of sedation, atropine, antacids or other commonly employed antiemetic measures were selected for treatment. Dehydration and electrolyte imbalance were corrected to as nearly normal as possible before therapy was initiated. This adjustment frequently brought about control of vomiting. However, if symptoms persisted, patients were then treated with chlorpromazine in a dose of 25 to 50 mg. intramuscularly four times a day, followed by 25 to 50 mg. by mouth four times a day, as soon as oral medication could be retained. It was also effective when given as a rectal suppository. Patients tolerated the drug exceedingly well. In no case was it necessary to discontinue chlorpromazine, although mild drowsiness occurred in some patients. Brief episodes of acute hypotension have been noted, and some observers have thought that a mild jaundice has been produced in a rare patient, but these complications did not occur in any of this series.

Table 2. *Effect on Electrocardiogram and Side Reactions.*

Patient	Electrocardiogram	Dosage of Chlorpromazine	Remarks
N.M.	Electrolyte imbalance; prolonged QT interval; left-ventricle hypertrophy.	— (None)	Serious nausea & vomiting
	Electrolyte imbalance; hyperkalemia; less prolonged QT interval.	25 mg. (3 times per day)	Complete freedom from nausea & vomiting; patient eating & reasonably comfortable.
J.P.	Prolonged QT interval and sharpening of T waves	— (None)	Severe nausea & vomiting
	No important changes	25 mg. (4 times per day)	No vomiting; patient still has nausea in morning.
W.E.	Normal	— (None)	Nausea & vomiting
	Normal	25 mg. (4 times per day)	Good appetite; patient feels fine & has no nausea.
S.F.	Short PR interval; possible hyperkalemia.	— (None)	Vomiting
	No change	25 mg. (3 times per day)	Good appetite; no nausea or vomiting.
J.M.	Sinoatrial block or sinus pauses	— (None)	Hiccuping, nausea & vomiting
	Potassium intoxication	50 mg. (3 times per day)	Patient still has hiccup, but no nausea or vomiting
R.K.	Left-ventricle hypertrophy & probably short PR interval (0.12 sec.)	— (None)	Nausea & vomiting
	Sinus tachycardia with digitalis effect	25 mg. (3 times per day by mouth)	Good appetite
M.A.	Changes compatible with localized pericarditis	— (None)	Anorexia, nausea & vomiting
	Left-ventricle hypertrophy	25 mg. (4 times per day)*	Patient able to eat & retain meals; some terminal nausea.
E.S.	Low electromotive force; PR interval, 0.21 sec.	— (None)	Nausea & vomiting
		50 mg., intramuscularly, followed by 50 mg., by mouth, every 6 hr.	Complete relief from nausea & vomiting
D.H.	Suggestive of hyperkalemia	— (None)	Vomiting
	Perhaps less hyperkalemia	25 mg. intramuscularly, followed by 25 mg. (every 6 hr.) by mouth	Good appetite
A.P.	Compatible with hyperkalemia	— (None)	Anorexia, nausea & vomiting
	Compatible with hyperkalemia	25 mg. (3 times per day)	Nausea & vomiting cleared
E.G.	Abnormal (nonspecific)	— (None)	Severe nausea & vomiting
	Sinus tachycardia, compatible with left-ventricle hypertrophy	50 mg. intramuscularly (4 times per day), reduced to 25 mg. (3 times per day)	Definite improvement
W.O.	—	— (None)	Severe nausea & vomiting
	—	50 mg. (4 times per day)	Complete relief
H.R.	—	— (None)	Severe nausea & vomiting
	—	50 mg. (4 times per day), increased to 50 mg. (6 times per day)	Good relief, with 50 mg. 4 times per day; complete relief on 50 mg. 6 times per day.
C.F.	QT interval 40% prolonged	— (None)	Nausea & vomiting
	No change	50 mg. (4 times per day)	Complete relief

*This patient maintained on chlorpromazine, 50 mg., 3 times per day, for 5 mo., with relief of nausea & vomiting, although blood chemical constituents abnormal. If drug omitted, severe vomiting ensued.

Results

It was apparent immediately that the drug was definitely effective in controlling the nausea and vomiting of uremia. Although not every case was completely controlled, it was obvious that all were benefited. Of the 14 patients who received the drug, all were completely relieved except 1, who was considerably improved. There were no complete failures when the drug was given in adequate amounts. The results are given in Tables 1 and 2.

Discussion

The beneficial effect of chlorpromazine was striking. Patients who had been depressed and anorexic, with nausea and vomiting, for days were relieved in two or three hours. Frequently, they ate their next meal—for some the first in two or three days. Usually, improvement in general condition resulted promptly. They became more cheerful, relaxed and physically stronger. With the disappearance of the nausea and vomiting management became much easier, and the electrolyte balance more stable. Some patients were maintained for weeks nearly free from any nausea or vomiting, although there were severe electrolyte disturbances.

It is apparent that elimination of the drug is not dependent on the kidney since there was no observable difference in degree of effect or dose required between patients with slight or no renal impairment and those with complete anuria.

About a fourth of the patients noted drowsiness after doses as small as 25 mg. four times a day. For the most part, however, this was not severe enough to present a problem. The drowsiness is similar to that which follows the administration of diphenhydramine (Benadryl) and other antihistaminic drugs. It does not give complete relaxation, and some patients become restless and find that the drowsiness is unpleasant.

Pruritus, when not too severe, is frequently relieved. In this respect chlorpromazine behaves like drugs of the antihistaminic series, although it does not possess any observable antihistaminic action.

Summary

Chlorpromazine, a recently developed chlorinated phenothiazine (Thorazine), in doses of 25 to 50 mg. four times a day, was found to be effective in suppressing nausea and vomiting in 13 of 14 cases of severe uremia.

Drowsiness occurred in approximately 50 per cent of the patients. In no case was it necessary to discontinue the drug because of this effect.

Pruritus was frequently relieved. In this regard, chlorpromazine behaved like compounds of the antihistaminic series.

Elimination of the drug is not dependent on the kidneys.

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USE OF CHLORPROMAZINE IN RADIATION SICKNESS AND NAUSEA FROM OTHER CAUSES*

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RADIATION sickness has been one of the problems of the radiologist since the advent of x-ray and radium therapy more than fifty years ago. This effect is common, and occasionally is so distressing that it prohibits further treatment in spite of a desirable therapeutic response. Reducing the daily dose of radiation does not solve the problem, for, although nausea is less likely to occur with small doses, the series of treatments is thereby prolonged unduly, and may thus be of little or no benefit. Consequently, many preparations of widely varying character have been employed over the years in an attempt to combat the malaise, nausea and actual vomiting associated with a series of x-ray treatments. The preparations favored in recent years include vitamin supplements and the various fractions of liver extract. In this hospital nicotinamide has frequently been used in doses of 25 to 50 mg., three times daily, and although this therapy appears to have been of some value it has often left much to be desired.

In March, 1953, the opportunity of trying a new preparation, chlorpromazine,‡ often designated as Compound 2601-A or as 4560 R.P. and Largactil in the foreign literature, was offered. Chlorpromazine is chemically related to Phenergan and Diparcol, as shown by its structural formula (given in the preceding paper by Friend and Cummins).

The experimental work of Courvoisier and Fournel[1] had shown that this compound antagonized the action of apomorphine, a centrally acting emetic, and its possible usefulness in controlling irradiation was investigated. The drug was dispensed to patients experiencing nausea incident to continuing radiation therapy, and the results obtained over a course of nine months recorded.

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‡Kindly supplied as Thorazine by Smith, Kline and French Laboratories, Philadelphia.

Patients with mild to moderate symptoms were instructed to take one 25-mg. tablet before each meal. With this dosage the nausea and vomiting were readily controlled in almost all cases. After a short experience with this dosage it became apparent that 10 mg. before each meal was entirely adequate for the majority of the patients, and with this smaller amount of the drug there has been almost no complaint of drowsiness, of which a few patients had complained when taking 25 mg. three times daily. In recent months patients experiencing nausea incident to radiation therapy were tried first on a regimen of chlorpromazine, 10 mg. before each meal. If the nausea was not completely relieved, the dose was increased to 25 mg. before each meal. Patients with severe vomiting (which had been present before the x-ray treatments were started in most cases) were given 50 mg. intramuscularly once or twice daily. As soon as the severe symptoms were controlled the medication was given by mouth.

Table 1 summarizes the clinical characteristics of the 84 patients in this series and the effect of chlorpromazine on the nausea secondary to x-ray therapy.

TABLE 1. *Effect of Chlorpromazine on the Nausea Secondary to X-Ray Therapy.*

DIAGNOSIS	NO. OF PATIENTS	COMPLETE RELIEF	MODERATE RELIEF	NO RELIEF
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Metastases from carcinoma of breast	27	22	5	
Lymphoma	12	9	2	1
Leukemia	4	3	1	
Carcinoma of lung	9	7	1	1
Carcinoma of cervix	9	9		
Carcinoma of ovary	8	6	2	
Carcinoma of rectum	3	2		1
Carcinoma of bladder	7	6	1	
Carcinoma of gall bladder	1			1
Herpes zoster	3	3		
Osteogenic sarcoma	1	1		
Totals	84	68	12	4

All but 4 of 84 patients obtained moderate to complete relief of nausea. Never before had any preparation for combating irradiation sickness been used with such satisfactory results.

The response to 25 mg. three times daily by mouth was proportionately better than that to 10 mg. Optimum dosage, however, was best determined on an individual basis. In most cases it was possible to shift from the intramuscular to the oral route within a few days; however, 2 patients had to be continued on intramuscular medication for two weeks.

Most of the patients listed in Table 1 were given x-ray treatments daily except Sundays, and the average daily dose was 250 to 300 r, measured in air. Portals varied in size from 100 to 225 sq. cm. and were widely distributed over the body. In each of the 4 patients who were not benefited by administration of chlorpromazine the malignant tumor is known to have been widespread and to have involved the liver. It is assumed that the poor result may have been related to the hepatic disease. The liver itself was in the field of treatment only in the patient with recurrent and metastatic carcinoma of the gall bladder. The patients with herpes zoster, each of whom had unilateral involvement of the fifth cranial nerve, were treated with daily doses of about 120 r, measured in air, through ports 5 cm. in diameter. Nausea was present before radiation therapy was started and is assumed to have been due to the disease rather than to the radiation.

These results stimulated several members of the medical and surgical staffs to evaluate chlorpromazine in nausea and vomiting of diverse origin; Table 2 summarizes their results. Perhaps the most striking effects were those observed by Dr. James H. Tullis. Of 10 patients receiving nitrogen mustard for widespread lymphoma only 3 experienced the severe nausea and vomiting usually associated with the intravenous administration of that drug; 2 had no vomiting whatever, and 5 were troubled in only a mild degree. It thus appeared that the use of chlorpromazine made the administration of the nitrogen mustard much easier for the patient.

Others on the staff reported beneficial results in relief of nausea and vomiting in patients with uremia, liver metastases, migraine and early pregnancy. Provocative, from the point of view of surgery, is the fact

TABLE 2. *Effect of Chlorpromazine on Nausea not Related to X-Ray Therapy.*

DIAGNOSIS	NO. OF PATIENTS	COMPLETE RELIEF	MODERATE RELIEF	NO RELIEF
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Lymphoma (patient receiving nitrogen mustard)	10	3	5	2
Metastases to liver	6	3	3	
Postoperative state	3	3		
Uremia due to diabetic nephropathy	1		1	
Migraine	1	1		
Pregnancy, early	2	2		
Totals	23	12	9	2

that chlorpromazine appears to inhibit postoperative vomiting. Three patients recovering from upper abdominal operations, whose vomiting had become a serious problem, were successfully managed with doses of this compound. Friend and Cummins,[2] in a more extensive series, and recently Kent et al.[3] have reported their evaluation of chlorpromazine as an antiemetic agent.

CONCLUSIONS

From these results in 84 cases of irradiation sickness and those of colleagues in 23 cases of nausea and

vomiting, it is evident that chlorpromazine can be a valuable drug. Its further study on an objective basis is warranted.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40231

Presentation of Case

First admission. A sixty-year-old retired ink-factory worker was admitted to the hospital because of atrial fibrillation.

Five years previously the patient noted fatigue and "sweats" lasting for a few months and a hacking cough diagnosed as "flu." There was a similar episode two and a half years before admission. A month later he stopped working because he was "tired" and did not feel "up to his job." At night he had some difficulty in breathing, which he blamed on "clogging up" of his nose. He was seen by his physician, who noted ankle edema and referred him to the Emergency Ward. Examination revealed atrial fibrillation and congestive heart failure; both were treated by the usual methods, with good response. An electrocardiogram showed atrial fibrillation and an uncontrolled ventricular rate, with no evidence of myocardial infarction. On discharge he had atrial flutter with a 2:1 heart block. He was placed on a regimen of digitoxin and ammonium chloride. He was readmitted to the Emergency Ward a week later because of atrial flutter and fibrillation that had not responded to digitalis given to limits of toxicity, and quinidine, 0.2 gm. four times a day, in addition to full digitalization, was therefore started. Since then, he had been followed in the Medical Out Patient Department, where treatment consisted of digitoxin and Mercuhydrin; he seemed to be under good control as far as the heart rate was concerned. His only complaints were sweating, fatigue and occasional episodes of paroxysmal nocturnal dyspnea. Three basal metabolic rates were reported as +19, +15, +13 per cent. The protein-bound iodine was 4.9 gamma per 100 cc., and the radioactive iodine uptake was 27.1 per cent in forty-eight hours. During the succeeding months fibrillation continued but without complaints of dyspnea, orthopnea or chest pain.

There was no history of rheumatic fever, coughing, pleurisy or alcoholism.

Physical examination revealed an obese man in no discomfort; he was not orthopneic or dyspneic. The neck veins were not distended, and the thyroid gland was not enlarged. The chest was clear but increased in anteroposterior diameter, with some limitation of diaphragmatic motion. The heart was enlarged, the border of dullness extending 2 cm. beyond the midclavicular line. The rate was 140, with runs of regular and irregular rhythm. There was a Grade 1 apical systolic murmur. The liver edge was palpable 1½ fingerbreadths below the right costal margin.

The temperature was 98°F., the pulse 140, and the respirations 18. The blood pressure was 140 systolic, 85 diastolic.

The urine had a specific gravity of 1.028 and gave a + test for albumin and a brown-orange reaction for sugar; there were occasional white cells in the sediment. Examination of the blood showed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 14,100, with 80 per cent neutrophils. The fasting blood sugar was 275 mg., and the nonprotein nitrogen 38 mg. per 100 cc. The prothrombin time was 18 seconds (normal, 13 seconds). A roentgenogram of the chest revealed cardiac enlargement, predominantly ventricular, and a slight degree of pulmonary congestion (Fig. 1). Fluoroscopic study suggested some calcification in the mitral valve not seen on x-ray examination.

An electrocardiogram on the second hospital day disclosed atrial flutter and fibrillation and digitalis effect. On a second tracing two days later atrial flutter with a 2:1 block and intraventricular conduction delay, probably of the right-bundle-branch-block type, were noted. On the eighth hospital day atrial flutter with a 3:1 and 4:1 block and intraventricular block with digitalis effect were present. Quinidine treatment was given, and in twenty-four hours the cardiac rhythm reverted to normal, at a rate of 100. On the following day rhythm was again irregular at a rate of 104 with runs of regular and irregular rhythm.

There was persistent leukocytosis (white-cell counts of 12,000 to 18,000) until the day of discharge. The patient was discharged on 20 units of protamine zinc insulin, Gantrisin, digitalis and quinidine.

Final admission (eighteen months later). Shortly after the previous discharge, on digitoxin and quinidine therapy, the heart rhythm reverted to normal at

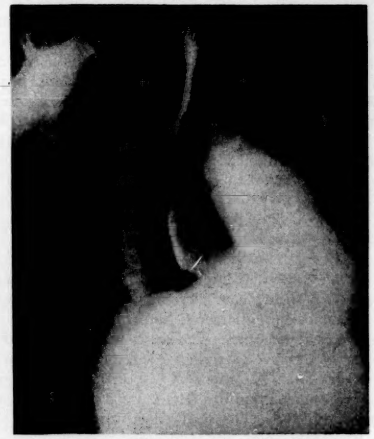

FIGURE 1. *Roentgenogram of the Chest. Right anterior oblique view shows considerable enlargement both anteriorly and posteriorly.*

a rate of 80. Ten months later, the rhythm was again found to be irregular, but there were no signs of congestive heart failure. The radioactive iodine uptake at that time was 27.8 per cent. Seven months later ankle edema was noted, and the liver edge was palpable 5 fingerbreadths below the right costal margin. On mercurial diuretics the congestive heart failure improved, but fibrillation continued. He continued to feel poorly with cough, weakness and choking sensations; three or four days before entry he was nauseated and vomited two or three times a day. For the first time, two days before admission, he also had blood-streaked sputum without chest pain or fever. The diabetes had gradually improved so that the fasting blood sugar was only 94 mg. per 100 cc. four weeks before admission.

Physical examination revealed a well nourished, apprehensive man with neck-vein distention up to 2 cm. on the left. There were dullness and decreased breath sounds in the right base and inspiratory rales at both bases. The heart was enlarged, and there was a Grade 2 or 3 apical systolic blow and an early diastolic gallop. The liver edge was palpable 9 cm. below the right costal margin, and there was +++ pitting ankle edema.

The urine gave a +++ test for albumin, a + test for acetone and a + test for bile; the sediment contained many fine granular and hyaline casts per high-power field. The hemoglobin was 16.5 gm. per 100 cc., the white-cell count 16,200, with 79 per cent neutrophils, and the hematocrit 63 per cent. The fasting blood sugar was 105 mg., the nonprotein nitrogen 54 mg., the bilirubin 1.9 mg., the total protein 5.9 gm., the albumin 2.4 gm., the globulin 3.5 gm., the serum iron 115 microgm. (normal, 125 to 280 microgm.), and the iron-binding capacity 265 microgm. per 100 cc.; the iron saturation was 43 per cent (normal, about 33 per cent). The sodium was 121 milliequiv., the potassium 6 milliequiv., the chloride 89 milliequiv., and the carbon dioxide 23 milliequiv. per liter.

An electrocardiogram demonstrated atrial fibrillation with uncontrolled ventricular rate. X-ray films of the chest revealed a greatly enlarged heart, with evidence of fluid in the right pleural cavity and an area of density in the right lower lobe (Fig. 2).

On the second hospital day a phlebotomy was done, after which the patient seemed comfortable although

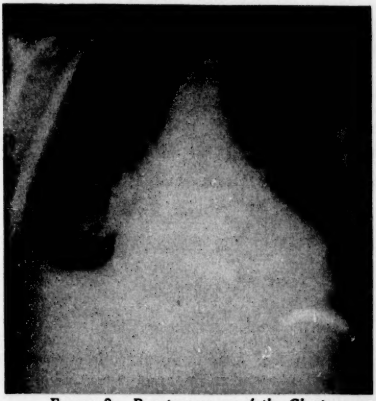

FIGURE 2. *Roentgenogram of the Chest. Arrow points to abnormal density at the right base.*

he continued to cough up small amounts of dark-red blood. Two days later the temperature rose to 103°F., and he complained of dull, nonpleuritic pain in the right side of the chest. Hemoptysis persisted. On the sixth hospital day bilateral femoral-vein exploration and ligation were performed but failed to show any thrombi. The next day, twelve hours after the venous ligation, he suddenly became cyanotic and unresponsive, the blood pressure was unobtainable, and he died a few minutes later.

DIFFERENTIAL DIAGNOSIS

DR. EDWIN O. WHEELER*: "The patient was discharged on . . . Gantrisin. . . ." I suspect that he was

*Assistant physician, Massachusetts General Hospital.

thought to have a urinary-tract infection; perhaps that accounted for the leukocytosis.

This is a case of congestive heart failure terminating four years after the onset of symptoms and complicated terminally by probable pulmonary embolism and infarction. The obvious problem is the cause of this man's heart disease. Are there any features in the record that help in diagnosis? The absence of some signs and symptoms is of value. In the first place he was not hypertensive at any time, so I can exclude hypertensive heart disease. He had no history of rheumatic fever, and when he was first seen in congestive heart failure he had no significant heart murmurs. It is true that toward the end of the illness a Grade 2 or 3 systolic apical murmur developed, but at that time there was no diastolic murmur. A diastolic gallop was heard terminally, suggesting that if an audible diastolic murmur had been present it would have been noted. Probably, the systolic murmur and gallop terminally were on the basis of cardiac dilatation and weakness. Rheumatic heart disease is unlikely. Finally, there was no history suggestive of angina pectoris or of myocardial infarction. I saw one of the electrocardiograms taken after the onset of congestive heart failure, in which the only abnormalities were in the rhythm and in the T waves; there was no evidence of myocardial infarction. One of the later electrocardiograms showed a conduction defect, probably incomplete right-bundle-branch block, with no definite evidence of myocardial infarction. In a man sixty years of age who is obese and has diabetes it is difficult to rule out coronary-artery disease. Statistically, coronary-artery disease should have been present but in the absence of angina or myocardial infarction I doubt if it was the cause of the congestive heart failure. Therefore, I can probably rule out the three common causes of congestive heart failure: rheumatic heart disease, hypertensive heart disease and probably coronary-artery disease, although the last I cannot be certain about.

It might be well to look at the x-ray films although I suspect that they are going to be helpful only in a negative way. I am interested in whether the patient had any specific chamber enlargement, calcification in the mitral valve or in the pericardium or evidence of pulmonary disease at the onset of trouble.

Dr. Joseph Hanelin: We have films extending over three years; in the earliest ones the cardiac enlargement is fairly marked. The pulmonary vessels are large and engorged at both lung roots, and the costophrenic sulcus on each side is blunted, possibly owing to small amounts of fluid.

Dr. Wheeler: Is there anything in the film to suggest pulmonary infarction except the fluid?

Dr. Hanelin: It is possible that there was some consolidation at the left base, but it is not confirmed by additional films and no comment was made about it at that time. Two years and four months later the heart is again huge and of about the same size. The right anterior oblique view particularly (Fig. 1), as well as the lateral view, shows considerable enlargement anteriorly so that there may well be a fair amount of enlargement of the right ventricle. There is also some enlargement of the heart posteriorly, which may or may not represent displacement of the left ventricle by the right ventricle or independent enlargement of the left ventricle. There is some fullness of the left atrium, but that is not prominent. Films made at the time of the last admission (Fig. 2) show the pronounced cardiac enlargement and the abnormal density at the right base, which has developed since the previous films. A day later the density appears somewhat smaller, and about two weeks later it has further cleared. This film, presumably made immediately before death, shows extensive abnormality throughout the right lung, with a great deal of engorgement of the vessels and what seems to be pulmonary edema and very likely free pleural fluid over the entire lung.

Dr. Wheeler: Does the change in this region of the right lung over the short period suggest a revolving pulmonary infarction?

Dr. Hanelin: It is entirely compatible with an infarct.

Dr. Wheeler: As I suspected, the x-ray films are not very helpful. They do not point definitely to any specific chamber enlargement; they probably suggest involvement of both right and left ventricles and that is borne out by the fact that the electrocardiogram did not give any clear-cut evidence of hypertrophy of the right ventricle.

Is there anything in the history that would lead me to suspect any of the less common causes of congestive heart failure, of which there are a great number? One point is the arrhythmia that the patient had from the time he was first seen. Arrhthmias with a rapid, uncontrolled ventricular rate occasionally lead to congestive heart failure, possibly in patients with normal hearts. However, although he had an arrhythmia off and on during his illness, the heart rate was under good control so that it seems unlikely that the arrhythmia was responsible for congestive heart failure. Could the episodes of arrhythmia have been the result of repeated pulmonary emboli, which occasionally precipitate bouts of atrial arrhythmia and which we have seen in some patients lead to hypertrophy of the right ventricle and congestive heart failure? He had no history suggesting acute pulmonary emboli, and there was no evidence of right-ventricle hypertrophy in the electrocardiogram. Except for the shadow present in the lung in the terminal illness there was no definite evidence of involvement of the lungs. Therefore, I think chronic cor pulmonale as a result of repeated pulmonary emboli is quite unlikely.

Another uncommon form of heart disease that was obviously suggested to the physicians who took care of him was thyrotoxicosis. He gave a history of sweating and fatigue, and he had an atrial arrhythmia,

flutter and fibrillation, which was difficult to control. Several basal metabolic rates and a radioactive iodine uptake were normal. Aside from the fatigue, sweating and arrhythmia there was nothing to suggest thyrotoxicosis on clinical examination, and the laboratory examinations seem to have ruled that out.

The patient had diabetes and evidence of abnormal liver function. Could he have had hemochromatosis, which can sometimes lead to congestive heart failure? Against this diagnosis are the absence of pigmentation, the easily controlled diabetes — as a matter of fact the diabetes seemed to be less severe as time went on — and the normal serum iron values. In all probability the abnormal liver-function tests could be explained by congestive heart failure so I doubt that hemochromatosis was present.

Constrictive pericarditis is an uncommon cause of congestive heart failure. The absence of certain signs make me think he did not have that: the venous pressure, at least as judged by the neck veins, was normal after the onset of the congestive heart failure, a paradoxical pulse was not mentioned, no calcification was seen in the pericardium, and on fluoroscopic study constrictive pericarditis was not suspected. Furthermore, he did not have striking right-sided heart failure during the course of the disease. I think I do not need to consider pericarditis very seriously.

There are other uncommon forms of disease that lead to congestive heart failure, but I have no definite reason to suspect them. Primary amyloidosis, for instance, may be manifested by congestive heart failure. No mention of a large tongue was made, and amyloidosis was not seriously suspected, for no biopsy was done.

Finally, there is a rather ill defined group of diseases that may cause congestive heart failure and are difficult if not impossible to diagnose ante mortem. In the past these have been listed as Fiedler's myocarditis, idiopathic cardiac hypertrophy and, more recently, subendocardial fibroelastosis. It has become obvious that Fiedler's myocarditis is rarely if ever seen — at least rarely discussed in these sessions — and that some of the cases that were considered to be idiopathic hypertrophy in the past were actually subendocardial fibroelastosis. Subendocardial fibroelastosis appears to be the commonest of the group at present and is a fairly well defined pathologic entity. How to establish that diagnosis clinically is another matter since there is nothing especially characteristic about the clinical course of the disorder. It should be suspected in the absence of any other known causes of congestive heart failure. Patients with subendocardial fibroelastosis often have arrhythmias, conduction defects, congestive heart failure and, of course, peripheral emboli. This patient had no evidence of peripheral emboli. If he had had peripheral emboli I should believe that subendocardial fibroelastosis was an excellent possibility.

I do not think I need consider seriously the other uncommon diseases that lead to congestive heart failure. There is little in the record to suggest them. I am not happy with any diagnosis, but I am inclined to believe this patient probably had subendocardial fibroelastosis as the cause of the congestive heart failure. I should not be surprised if he had coronary-artery disease although I doubt if it was the cause of the congestive heart failure. I suspect that the terminal illness was due to pulmonary emboli.

DR. BENJAMIN CASTLEMAN: Dr. Palmer, you saw this patient.

DR. ROBERT S. PALMER: I saw him eight days before he died. At that time he had congestive heart failure, with an uncontrolled heart rate. Our investigations indicated that he did not have thyrotoxicosis, and, like Dr. Wheeler, we concluded that he had one or another of the contributing causes of intractable heart failure—namely, infarction of the myocardium, pulmonary emboli or infection. I believed the most likely was pulmonary emboli. I contented myself with saying that he might have one of the other rare causes of congestive heart failure without going into detail. The only question in my mind was whether the veins should have been tied sooner or not at all.

DR. HOWARD B. SPRAGUE: I thought that perhaps the pulmonary episodes that he had some time before indicated that he had chronic repeated emboli with cor pulmonale.

DR. PALMER: We thought that clinically he had some emphysema as well, but that was not apparent on x-ray examination.

DR. WALTER BAUER: I was greatly impressed with Dr. Wheeler's thorough discussion of the possibilities.

CLINICAL DIAGNOSES

Atrial fibrillation.
Heart disease, etiology unknown.
Pulmonary emboli.

DR. EDWIN O. WHEELER'S DIAGNOSES

Subendocardial fibroelastosis.
Pulmonary emboli.

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral insufficiency.
Pulmonary embolism, old and recent.
Bronchopneumonia.
Phlebothrombosis, deep and common femoral veins, right.
Mural thrombus, right ventricle.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: I suppose that, during the last two years, we have had at least half a dozen cases in which the cardiologists went through a differential diagnosis without being able to select one diagnosis and therefore ended up with the vague group that we

have now collected and called fibroelastosis of the endocardium*; this condition usually involves the left ventricle, but it may involve the right and may often cause mural thrombi that produce emboli to both circuits. That is what we expected to find in the case under discussion.

The heart weighed 600 gm. The right ventricle was of good size; it was hypertrophied and somewhat dilated. In the apex was a mural thrombus that was firmly attached, and I doubt whether any fragments broke off from it. The left ventricle was also large, and, if one wants to stretch a point, there was slight opacity to the endocardium.

On microscopical sections we did find slight thickening of the endocardium, with some fibroelastosis, but I do not believe it was sufficient to put this case into the group of idiopathic cardiac hypertrophy with fibroelastosis. There was disease of the mitral valve: the leaflets were thickened, and the chordae tendineae were also thick and shortened. Although thickened the leaflets were large, and I believe there might well have been a fair amount of insufficiency, with little if any stenosis. The left atrium was quite large—perhaps some of the shadow seen in the x-ray films was the left atrium extending posteriorly against the spine. There was very mild coronary-artery disease without any evidence of occlusions and only a little fibrosis of the myocardium. I am inclined to conclude that the basic cause of this patient's heart disease was rheumatic infection of the mitral valve, with a pure regurgitant mitral valve, a condition in which the heart is very large. A mural thrombus in the right ventricle is occasionally seen in patients who have arrhythmias; this patient had had fibrillation for years.

The patient died with a massive pulmonary embolus, and there was evidence of previous embolic infarction in the right lower lobe. In addition there was a tremendous amount of bronchopneumonia, with breaking down of alveolar walls and the formation of abscesses. I think most of what was seen in the last film taken before death was severe bronchopneumonia, with abscess formation. These were not septic infarcts; the infarcts that were present were of the bland variety. The surgeon had tied both superficial femoral veins at their junction with the deep femoral veins. On examining these veins we found no evidence of any thrombus on the left side. On the right side, however, the deep femoral vein contained a thrombus that extended up into the common femoral vein, and I believe that was the source of the terminal massive embolism.

Should you like to comment any further, Dr. Wheeler?

DR. WHEELER: It is hard to believe that this patient had severe mitral regurgitation when he first came in with congestive heart failure.

*Thomas, W. A., Randall, R. V., Bland, E. F., and Castleman, B. Endocardial fibroelastosis: factor in heart disease of obscure etiology: study of 20 autopsied cases in children and adults. *New Eng. J. Med.* (in press).

DR. CASTLEMAN: He had fibrillation and flutter all the time. Could that have masked it?

DR. WHEELER: I do not think so. There may be a tight mitral stenosis without a murmur but marked mitral regurgitation without a murmur is most unusual.

DR. SPRAGUE: There was more than one thing wrong with the heart, I think, and I agree that the mitral valve was abnormal.

DR. CASTLEMAN: The cause of death was certainly the embolism and the severe pneumonia.

DR. PALMER: Would Dr. Bauer have tied the leg veins earlier, or would he have used an anticoagulant?

DR. BAUER: I am sure that there are many days when I should not advise ligation and others when I should.

DR. PALMER: It is difficult to know if the tying of the veins earlier might have given some respite from congestive heart failure. I think we should have been alerted sooner about multiple pulmonary emboli and done something about it.

DR. CASTLEMAN: The patient had had infarcts before, and I do not believe the source was the right ventricle because the emboli were very small, suggesting that they came from the leg veins.

DR. BAUER: How about some months before?

DR. SPRAGUE: With these electrocardiographic changes—namely, incomplete right-bundle-branch block—it seemed to me that the right ventricle was very large, as it appears in the x-ray films.

DR. WHEELER: He had had right-bundle-branch block for a year and a half before he died. One of the electrocardiograms showed it.

DR. SPRAGUE: He started having the pulmonary trouble five years before he died.

DR. WHEELER: There was nothing that suggested old emboli?

DR. CASTLEMAN: No.

DR. WHEELER: The pathological findings and the history suggested that the emboli were not more than a month old. They were the cause of death.

DR. JACOB LERMAN: What did the kidneys show?

DR. CASTLEMAN: They were normal.

CASE 40232

PRESENTATION OF CASE

A thirty-five-year-old laborer was referred to this hospital three days after falling from a ladder.

The patient was at work when he fell about 25 feet, striking a steel beam with the left arm and landing on the left side. He was treated at another hospital, where both arms were put in casts and the left leg placed in traction for fractures. He was also told that "two or three ribs" were broken. He had pain in the middle and left sides of the chest with cough and respirations but denied abdominal or shoulder pain, dyspnea, palpitation and hemoptysis. Although he

required catheterization for voiding after the accident for a day or two he denied gross hematuria.

Twelve years before admission he had had a back injury, of unknown type, which was treated with bed rest, heat and massage for about two weeks. He improved and had no further symptoms.

Physical examination revealed the casts and traction as mentioned. The patient was in moderate distress. There was tenderness over the fifth to the eleventh rib on the left, with a questionable elevation of the left leaf of the diaphragm. The abdomen was slightly distended and tympanitic, with tenderness in the left flank and left lower rib cage. No organs were felt; peristalsis was normal.

The temperature was 98.6°F., the pulse 76, and the respirations 20. The blood pressure was 126 systolic, 86 diastolic.

The urine was cloudy amber, had a specific gravity of 1.028 and was otherwise normal except for the sediment, which contained rare red cells, rare white cells, mucin and amorphous material. The hemoglobin was 12.8 gm. per 100 cc., and the white-cell count 6400, with 64 per cent neutrophils, 24 per cent lymphocytes, 5 per cent monocytes and 7 per cent eosinophils.

The patient did well with procedures to correct bony deformities and physiotherapy to return function. On the thirty-fourth hospital day slight epigastric and left-upper-quadrant pain began, radiating to the left scrotum and to the rectum. He felt the urge to defecate and had a bowel movement without pain or blood; the stool was loose but was otherwise normal. While returning to bed, he felt weak, fainted and had an involuntary stool. Examination at that time showed him to be cold and clammy. The blood pressure was 110 systolic, 65 diastolic, and the pulse 82. The pupils were equal, round and regular and reacted to light. There was discomfort to palpation in the epigastrium, but the remainder of the abdomen was soft and nontender. He denied pain. The white-cell count was 19,500, with 86 per cent neutrophils, 5 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils; the hemoglobin was 12.4 gm. per 100 cc. During the next three or four hours he noted that he had pain in the left shoulder when lying down and pain in the pelvis and rectum when erect. He had slight pain in the left lower part of the chest and was most comfortable in the left decubitus position. Five hours after the onset of the pain examination showed him to be pale but less sweaty. The blood pressure was 96 systolic, 70 diastolic, the pulse 110, and the respirations 20. There was some pain in the left lower part of the chest with respirations, but the chest was clear. The heart sounds were distant but normal. The abdomen was slightly distended, with reduced peristalsis. There was generalized rigidity and tenderness, more marked in the left upper quadrant but present in the right lower quadrant as well, and marked rebound tenderness. Rectal examination was negative. X-ray films showed the splenic shadow to be more prominent than usual, but no definite indentation of the stomach was seen. X-ray films of the chest were not remarkable except for the fractured ribs as noted before. An operation was performed.

Differential Diagnosis

Dr. Robert S. Shaw*: In summary, this thirty-five-year-old man had severe trauma to the left lower part of the chest and left upper quadrant of the abdomen without any localizing signs of injury within the peritoneal cavity. He did well for thirty-four days without symptoms suggesting disease in the abdomen and then suddenly had evidence of a peritoneal irritation in the left upper quadrant. He presented hyperperistalsis followed by ileus, which is quite characteristic of sudden peritoneal insult and is frequently seen after perforated peptic ulcer. There was evidence in the shifting pain in the shoulder and pelvis that the irritant was a fluid sufficiently abundant to move about the peritoneal cavity with change in position. The fluid was blood in all probability because of the gradual appearance of hemorrhagic shock. One immediately considers a secondary hemorrhage from an injured spleen, and I have to strain to consider other diagnoses.

Conceivably, the shock could have resulted from a secondary rupture of a traumatic cyst of the pancreas. That seems unlikely because such an injury of the pancreas requires direct trauma and there would have been symptoms referable to the epigastrium, which were absent in this patient.

Since I have been in the aneurysm business recently I wonder about the possibility of secondary hemorrhage from a traumatic aneurysm of the aorta. Again, injury to the aorta always follows direct trauma to the vessel, usually in the lower abdomen. Gonzales and his co-workers[1] cited a case of a patient whose ruptured abdominal aorta resulted from his being struck in the exposed abdomen by falling plaster while he was lying supine and unconcerned in bed. Here, again, direct trauma and local signs are lacking in the case under discussion.

It is possible that the left kidney was injured. The trauma was in the appropriate region, and there were a few red cells in the urine. The presence of a few red cells is quite consistent with repeated catheterization in a man. However, the picture of a disaster occurring thirty-four days after injury does not fit with renal injury, which results either in immediate extravasation of blood or urine or in later sepsis.

I think I had better confine my discussion to a delayed rupture of the spleen. Rupture of the spleen can be divided into two main types, according to the nature of the injury: that with a rent in the capsule and that with an intact capsule. Most ruptures of the spleen involve a wound in the capsule, with continued,

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severe hemorrhage until the process is interrupted by death or by operation. If the wound in the spleen involves the hilar structures bleeding does not stop. However, hemorrhage from a laceration or split of the spleen on its convex surface, where the primary force of a blow is received, may be stopped by normal hemostatic mechanisms for a time if the wound is not too large. Later, because of the extreme friability and lack of fibrous cohesion of the spleen, secondary hemorrhage can take place and can be massive. If a patient has such a small tear in the capsule, he will be left in the quiet interval with a perisplenic hematoma and a certain amount of free blood in the peritoneum. This I should expect to cause more abdominal signs than this man had. He had neither evidence of general peritoneal irritation nor persistent signs in the left upper quadrant. Most discussions of the clinical entity stress the importance of persistence of left-upper-quadrant tenderness in the diagnosis of delayed rupture or impending rupture of the spleen. I think it is unlikely that this was a capsular break.

It could, however, have been an injury to the spleen that did not penetrate its capsule—a subcapsular hematoma or an intrasplenic hematoma. Intrasplenic hematomas can heal with fibrosis and organization, causing a white splenic tumor, or go on to cyst formation and secondary rupture. A subcapsular hematoma is characteristically a progressively enlarging blister under the capsule of the spleen. The capsule is attached to the spleen very lightly, and as the pressure from the hematoma increases, more capsule is pushed away from the spleen and more hemorrhage takes place. The end result is that the entire capsule is lifted away from the spleen proper by hematoma around to the hilus. The spleen may then be many times its normal size. When the capsule finally ruptures, the appearance at post-mortem examination or at operation suggests that the rupture occurred with explosive violence—the spleen being found in many fragments. This is probably because the spleen was initially fractured and held together only by the capsule. May I see the spleen in the x-ray films? If it is very large, I think we should consider this possibility. Against the possibility is the absence of persistence of the left-upper-quadrant tenderness. I should expect a growing hematoma to cause more signs and symptoms than this man had.

Dr. C. C. Wang: A single chest film shows no abnormality in the lungs; the heart appears normal. No fluid is definitely seen in the pleural space. Both leaves of the diaphragm lie in normal position. A film of the upper abdomen demonstrates considerable enlargement of the splenic shadow, which can be easily outlined; the renal outlines and the psoas-muscle shadow on the left also appear normal. No evidence of retroperitoneal hemorrhage can be recognized. The greater curvature of the stomach shows nothing unusual.

Dr. Shaw: Would you say that the splenic outline is clear, or can there be a hematoma around the spleen?

Dr. Wang: I do not see any evidence of hematoma around the spleen.

Dr. Shaw: That just shows the lower pole.

Dr. Wang: The medial pole of the spleen can also be outlined, and the fractures of the eleventh and twelfth ribs can be seen.

Dr. Shaw: A fractured rib near the spleen is not essential to the diagnosis of ruptured spleen but occurs in about a third of the cases. I do not think the splenic shadow is large enough or well enough outlined to be a bag of blood from a large subcapsular hematoma.

The other possibility, which better fits this story, is that of a relatively minor injury to the spleen with a small subcapsular hematoma that did not progress in the fashion mentioned. Such a hematoma might grow to a relatively small size and remain fairly stable for a long period, thereby causing nothing in the way of symptoms in the left upper quadrant and, not having bled, causing no general abdominal signs. This small blister on the surface of the spleen would eventually rupture both because the tension within the hematoma was gradually increased by the same mechanisms active in subdural hematomas and because the splenic capsule overlying it was deprived of its normal blood supply. I think the late time of rupture would support a diagnosis of a relatively minor, stable injury to the spleen such as a small subcapsular or intrasplenic hematoma. Secondary rupture of a spleen nearly always occurs between the third and ninth days and very rarely after two weeks. McIndoe[2] reports a case that occurred six months after the original injury. In conclusion I shall say that this man had a small subcapsular or intrasplenic hematoma on the convex side of the spleen and had bled secondarily from it.

Dr. Gordon A. Donaldson: Is there any explanation for the ureteral radiation of the pain?

Dr. Shaw: That bothered me. I wondered if he had scrotal hernia into which blood trickled. I assumed that symptoms resulted from intraperitoneal blood shifting down to the pelvis.

Dr. Donaldson: The episode in the hospital was dramatic. The patient was leaving the bathroom when the pain occurred. The pain was so severe that he fell to the floor and shortly went into a state of shock. Through the heroic efforts of the house staff he was resuscitated. When I saw him four hours later he had stopped sweating; it was obvious that an acute abdominal episode of some sort had occurred. I was somewhat surprised that time and effort were taken for x-ray study because he was in a precarious state. We were concerned, however, about the distribution of the pain. The left-shoulder discomfort was expected, but we could not explain the pain in the scrotum and also in the perineum; I mention this pain to

clarify our preoperative diagnosis. We operated on him about five hours after the onset of the dramatic collapse in the hospital corridor.

Clinical Diagnosis

Late rupture of splenic hematoma.
?Perforated ulcer or perforated viscus.

Dr. Robert S. Shaw's Diagnosis

Late rupture of subcapsular or intrasplenic hematoma.

Anatomical Diagnosis

Subcapsular and intrasplenic hematomas, with delayed rupture.

Pathological Discussion

Dr. Donaldson: At laparotomy we found about half the patient's blood volume in the abdominal cavity. Approximately 2000 cc. of free blood was aspirated from all quadrants of the abdomen, and in addition 1200 to 1500 cc. of clotted blood was removed from the left side of the abdomen and pelvis. A lemon-sized mass was found on the surface of the spleen. It was obvious that the splenic capsule had torn and that this was the source of blood loss.

Dr. Benjamin Castleman: Was the lemon-sized mass anterolateral?

Dr. Donaldson: Yes.

Dr. Castleman: The cut surface of the spleen fits Dr. Shaw's predictions. There were several intrasplenic hematomas and the extension of the hematomas into the splenic pulp was probably slow. Microscopical sections of the splenic pulp away from the hemorrhage do not show any condition that might have been a predisposing factor to rupture of the spleen such as infectious mononucleosis.

Dr. Donaldson: Do you think the straining at stool had anything to do with the rupture?

Dr. Castleman: I had planned to ask you that question. Did he build up enough intra-abdominal pressure to cause the rupture?

Dr. Shaw: I should suspect that increased intra-abdominal pressure would support the hematoma rather than precipitate rupture. In the material that I looked up I did not find any particular correlation of effort or secondary trauma with a secondary rupture.

Dr. Castleman: This is the longest delay of rupture that I can recall having seen in this hospital.

Dr. Robert S. Palmer: Perhaps the patient was palpating his own abdomen. I knew a patient who was found dead in bed from a ruptured spleen; he had a very large spleen from leukemia and was fond of palpating the large mass.

Dr. Shaw: McIndoe's[2] series is the one most often mentioned in the literature. He collected 47 cases; in the vast majority the rupture occurred within the first two weeks, but in 3 or 4 it occurred at about thirty days. As previously mentioned it was six months after injury in 1 case.

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NATIONAL SECURITY AND ILLEGAL DIATHERMY EQUIPMENT

THE Federal Communications Commission issued a public notice on February 19, 1954, entitled "The Enforcement of the Commission's Rules Regulating the Operation of Medical Diathermy Equipment," warning that operation of diathermy equipment of a type not approved, certified or licensed in accordance with the Commission's rules has been illegal since June 30, 1953. Actually, these rules went into effect on June 30, 1947, with six years allowed to owners of existing equipment to amortize their investment and acquire type-approved apparatus or to correct existent equipment for certification. A $10,000 fine and two years in jail now face the illegal operator.

Radiation from medical diathermy equipment can result in harmful interference with the nation's various radio-communication services. It is, in effect, a radio transmitter whose influence can be felt hundreds of miles from its place of origin. Monitoring of an illegal diathermy machine in Miami detected its signals in Texas, Washington State and Delaware. This spurious radiation can cause interference with frequencies far removed from the one on which the equipment is operating.

The importance of eliminating the estimated 20,000 illegal diathermy machines is obvious since they represent a threat to the national defense, local safety and security services and transportation services on land, sea and in the air, as well as an interference with radio and television programs.

Both planes and missiles can be guided to their targets by following radio signals. The United States has instituted the CONELRAD (CONtrol of ELectromagnetic RADiation) program to minimize the usefulness to an enemy of radio signals originating in this country. Diathermy apparatus operating outside this safeguard could be used to direct enemy bombers or guided missiles to their targets, and defensive guided missiles and protective networks could be interfered with at this crucial moment. Police and fire protective services, as well as civilian defense, depend substantially on radio intercommunication systems that may be affected by uncontrolled frequencies of diathermy machines. The latter could compromise the effective use of radio as an essential navigational and communication aid in air, ship and even train travel.

The potential hazard of the illegal diathermy machine is so far reaching, affecting as it does so many facets of modern life and even threatening the ability of mankind to survive in this confused world, that every step should be taken to eradicate this menace. It seems unlikely that the informed physician will fail to co-operate with the Federal Communications Commission, when his own welfare, as well as the lives of his countrymen, is at stake.

THE *PRACTITIONER* ON SEX

THE story of the young man who was taking a word-association test will no doubt be recalled by many readers. Regardless of their apparent lack of relation each word suggested to him the idea of sex and sex alone. When at the end of the test he was asked to explain this curious single-mindedness the reason became transparent; sex was all he ever thought of. One is occasionally reminded of the aphorism that sex, under the more euphemistic term of "love," is believed to make the world go around; if so then the *Practitioner*, in its April issue, has given the globe a faster spin.

The *Practitioner*, in this number, has done a service to all its readers by bringing into the open many of the imperfectly understood or even consciously misunderstood problems of amativeness, and supplying for the questions that they raise answers as satisfactory as possible. In the search for these solutions seventeen authorities have been selected to cast light from various angles on a variety of problems; almost as an invocation the attitude of the Church of England is first presented by the Bishop of Rochester. The Church

disapproves of promiscuity, of divorce and, in principle, of contraception. Heterologous artificial insemination is regarded as adultery and the product of conception as illegitimate. The homosexual temperament requires understanding and sympathy; homosexual practice is regarded as a sin and a perversion.

The problem of homosexuality is further considered in its entirety by C. G. Learoyd, who, discussing "the puppy prurients," concludes that even certain scientific studies of sex may have the effect of pornography. "It would have been a cleaner world," he believes, "if Kinsey had stuck to his rats." One is reminded of Mencken's criticism of the children's book designed to elucidate the facts of life, which described propagation in terms of bees and flowers; it did not so much render sex "clean," in his opinion, as it made botany salacious.

Under adverse circumstances, according to Learoyd, natural affections may be degraded into homosexuality. The devastating factor in homosexuality is its communicability, which is the main argument in favor of isolation. No good can come from herding trapped homosexuals into prison, which increases their degradation; better a "not unpleasant camp with kindly wardresses."

Viewing them from the medical aspect W. Lindesay Neustatter finds that homosexuals do not differ greatly in other respects from the average run of citizens, nor does he believe that "a moral rot" is setting in in the country. Like Learoyd he recommends a humane attitude, recognizing the need sometimes for segregation of the pervert to protect the community. The Constable of Nottingham, on the other hand, frowns fiercely on sex aberrations of all sorts, holding strongly to his belief, as one of his fellow countrymen expressed it, in the efficacy of the birch.

Other subjects discussed, in the main with clarity and wisdom, are premarital chastity, prostitution, sex problems in marriage, the etiology and treatment of impotence, problems of the unmarried woman, the celibate male and the adolescent, adjustments at the climacteric, sex and the elderly and the problems of sex in the services.

It can scarcely be doubted that premarital chastity is on the decline. Certainly England, with an estimated 70,000 illegitimate children fathered by members of the United States armed forces, has ample evidence of this probability. That the situation merits grave concern must be the conclusion of everyone who agrees that a high moral standard "is necessary for the fullest development of both the individual and society."

S. BURT WOLBACH, M.D.

1880-1954

In an appraisal of Simeon Burt Wolbach's* worth, one is tempted to emphasize his humanity, his colorful personality, his resourcefulness as an administrator, his decisive impact upon the minds of his students, his wide scope of interest—and lose sight of what will remain of enduring value, his contributions to science. These were distinctive and important, both in actually adding to the body of scientific knowledge and in transforming pathology from an inert and descriptive science to one alive and replete with logic and reasoning. He was not content with mere description or cataloguing of morbid anatomic details. His clear and incisive intellect penetrated to the core of histologic sequences and structural relations at the cellular level.

This attitude was expressed even during his early years as an investigator when the study of the pathogenesis of the rickettsial diseases was his major effort. In the Harvey Lecture, delivered in 1921 on the subject "Typhus and Rickettsia," he states:

> . . . in tissue reactions we find evidence for the classification or the grouping of diseases and from them may sometimes predict the probable nature of the exciting agent. Our knowledge of histopathology is now sufficiently complete to warrant formulation of a few criteria for prediction. I was almost tempted to say laws—but I shall say *invariable histological sequences.*

In the years devoted to vitamin research, a period dating from 1922 until his death on March 19, 1954, he again demonstrated his ability to separate essence from attribute in the solution of problems. Thus, he was not content until he could understand and summarize, in almost a single sentence, the basic process involved in a morphologic state, beautifully illustrated by his studies of scurvy, in which he showed that what appeared to many to be lesions of multiple character were essentially the failure of a single process—the inability of mesenchymal cells to lay down intercellular substances. He elucidated the fundamental fault in vitamin A deficiency as "loss of specific (chemical) functions of the epitheliums concerned, while the power of growth became augmented"—thus resulting in a keratinizing metaplasia. He showed that the nervous lesions of this deficiency were "purely of mechanical origin, the genesis of which is a disproportionate growth of the central nervous system in relation to the bone which surrounds it." It was his emphasis on the acceleration of normal growth sequences of bone that explained the bony changes seen in vitamin A intoxication.

One can say of this man that he was pre-eminently interested in a search for the truth, a striving for a solution of the riddle of life and death. His ideas were based on keen observation and were brought together to form a beautifully integrated picture that showed both his critical and his imaginative faculties. These were his sustenance, his bread of life; they will remain and constitute his share of immortality.

*Shattuck Professor of Pathological Anatomy, Emeritus, Harvard Medical School.

The American Institute of Homoeopathy have obtained from Meissen, Germany, the birth-place of Hahnemann, a block of sienite for the Washington Monument.

Boston M. & S. J., *June 14, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CALLANAN — Eugene F. Callanan, M.D., of East Milton, died on May 21. He was in his forty-eighth year.

Dr. Callanan received his degree from Tufts College Medical School in 1932. He was a member of the staffs of the Boston City, St. Margaret's, Carney and Milton hospitals, and was school physician, St. Agatha's School, East Milton.

He is survived by his widow, a daughter, four sons, his mother and a sister.

WORTHY — William Worthy, M.D., of Roxbury, died on May 20. He was in his seventy-seventh year.

Dr. Worthy received his degree from the College of Physicians and Surgeons, Boston, in 1908. He was a member of the Bay State Medical Association.

He is survived by his widow, three daughters and a son.

BOSTON MEDICAL LIBRARY

RECENT ACCESSIONS OF INTEREST

Enciclopedia Universal Illustrada Europeo-Americana: Etimologías Sánscrito, Hebreo, Griego, Latín, Árabe, lenguas indígenas Americanas, etc.: versiones de la mayoria de las voces en Francés, Italiano, Inglés, Alémán, Portugués, Catalán, Esperanto. 88 volumes, including the appendix volumes and year books, Madrid: Espasa-Calpe, 1930-1942. This general encyclopedia is an excellent reference source. It is strong in biography. Within a week after it was acquired by the Library it was used to advantage in tracing an important anatomist and physician who seemed to be neglected in other biographic works.

The Cyclopedia of Medicine, Surgery and Specialties. Edited by George M. Piersol, M.D., and Edward L. Bortz, M.D. 14 volumes and index. 8°, bound. Philadelphia, 1952. Set $195. (Annual revision pages, $15; review service, $10; sold only by subscription.) This standard cyclopedia has been published for more than twenty years and has gone through a number of editions. This new edition is issued in a new format of the loose-leaf type, and it is planned to keep the material up to date by annual revisions of the text and by a supplementary review service. The text is not run solid as in previous issues, but each article heads a new page and is signed by its author. The editors are assisted by six chief associate editors and a large corps of associate editors representing the various fields of medicine and surgery. The text has been thoroughly revised and in some cases rewritten in accordance with the latest advances in medicine, surgery and the specialties. Emphasis has been placed on treatment. The arrangement is alphabetical by subjects, making for rapid and convenient use. References to the literature have been limited, when used, to recent and important contributions. Each article is written by an authority on his subject. The publishing is excellent in every way; the type is particularly good, and the illustrations adequate. Each volume has about 1000 pages of two-column material. The work forms a complete, compact, easily available reference source for the busy practitioner. It is a library in itself, and should prove valuable for rapid consultation.

Memoria del Primer Congreso Interamericano de Higiene, 26 Septiémbre-1 Octubré, 1952. 880 pp. 8°. Havana: The Congress, 1953.

This congress was held in honor of Dr. Carlos J. Finlay and of the fifteenth year of the Pan-American Sanitary Office. Delegates were present from all the Central and South American countries and from the United States.

Homenaje ofrecido a Teófilo Hernando por sus amigos y discípulos. 592 pp., 4°, with portrait. Madrid: Libreria y casa editorial Hernando, S. A., 1953.

Dr. Hernando, an outstanding physician of Spain, was born in 1881; he received his medical degree from the University of Madrid in 1907. He became an auxiliary professor of the faculty of medicine of the university in a short time and in 1911 went to Germany to do postgraduate work under famous professors (Schmiedeberg, Kraus, Albu and Kelling). He held many important medical offices in his country and was interested in fields outside his profession. He was at times president of the Junta de Investigaciones Cientificas, the Junta Protectora de las Bibliotecas y Archivos Eclesiásticas, the Asociación de Bibliotecarios, the Sociedad Española de Historia Natural and the Consejo Nacional de Cultura and vice-president of the Sociedad Española de Biologia. His varied interests are well illustrated by the numerous nonmedical positions of eminence that he held during his career. His last official position was that of president of the third international congress of therapeutics. He wrote many medical articles from 1905 to 1952.

CIVIL DEFENSE AGENCY

SIGNIFICANT FACTORS IN THE DEVELOPMENT OF A HOSPITAL DISASTER PLAN

THE tornado in June, 1953, required the hospitals in the vicinity of Worcester, without warning, to mobilize immediately, giving them an unprecedented opportunity to evaluate the effectiveness of their dis-

aster plans. They successfully mobilized their personnel and facilities to care for thousands of casualties.

Successful mobilization of a hospital to combat any sudden disaster can best be accomplished by previous detailed preparation. Disaster preparedness can only be developed and maintained by persistent awareness of the specific problems to be encountered.

Every hospital can develop its own comprehensive disaster plan for its personnel and facilities. To be effective a plan should be co-ordinated with those of all other hospitals in the surrounding area to assure the most effective use of all available personnel, facilities and supplies, and also with local civil-defense plans for communications, transportation and fire and police protection. Measures taken should be simple, flexible and practicable. Repeated drills and exercises are of great help in maintaining efficiency.

Two distinct phases should be considered:

I. Plans be put into operation should the hospital be directly involved in the disaster i.e. located within disaster area.
II. Plans be put into operation should the hospital not be involved in disaster but have as its function the reception and care of large numbers of casualties.

Plan I.—may involve several eventualities:

A. The warning of an impending attack does not provide sufficient time for evacuation, therefore, patients and personnel must seek protection within the hospital.
B. The warning of an impending attack does provide sufficient time for evacuation of patients and personnel.
C. Parts of hospital are damaged or personnel are unable to function.

Plan II.—will include the following eventualities:

A. General hospitals will be requested to receive and care for casualties up to several times their normal bed capacity.
B. Hospitals for nervous and mental disorders will receive and care for casualties in accordance with a special plan developed for this type of institution.
C. Hospitals for communicable diseases will expand to receive patients with communicable disease or victims of biological warfare.

The preliminary planning which is basic to a comprehensive disaster plan would include the following points:

1. The formation of a Disaster Committee within the hospital with the responsibility for developing, coordinating and perfecting a comprehensive disaster plan.
2. The development of a functional disaster organization to include:
   a. Director—in charge of disaster operations. The director would have the full authority for direction of personnel, supplies and facilities within the hospital during the emergency.
   b. Heads of services and other key hospital personnel and their alternates.
   c. A simple chain of command.
   d. The minimum essential functions that will be performed by each department, the persons who will perform these functions and the method by which these functions will be coordinated.
3. The development of a system of communications which will utilize all means available. Communications will be one of the most important functions to be performed. Service should include not only all areas within the hospital but strategic points outside the hospital. Because of the demand on community facilities prior arrangement with local civil defense director is imperative. Wherever possible, standing orders should be used for assembling both on and off duty personnel, volunteers and supplies.
4. The provision for substitutes or emergency sources of utilities:
   a. Electricity
   b. Water
   c. Heat
   d. Gas and refrigeration
   e. Sanitation

   The physical plant of the hospital must be kept in operation or brought back into operation as soon as possible. Additional utility services to operate the increased bed capacity of hospital will be needed.
5. The development of a plan for the evacuation of both patients and personnel:
   a. To be used in the event a pre-disaster evacuation is possible.
   b. To be used in post-disaster phases to provide accommodation for casualties. It is estimated that the clinical status of approximately 80% or more of inpatients in hospital would permit that they may be discharged to their homes or to nursing homes.

   These measures necessitate that pertinent clinical data of patients be readily available for evacuation purposes. Arrangements should be made now with local civil defense director for the development of general transportation plans.
6. Plans for the expansion of hospital facilities and services to care for casualties to include:
   a. Locating space within the hospital for litters and cots.
   b. Locating space in vicinity for litters, cots and related services.
   c. Expansion of nursing services by reassignment of nurses to provide wider coverage. Increase of staff would be accomplished through judicious use of nurses aides and volunteers.
   d. An increase in operating room and related services to care for large number of casualties requiring immediate surgery (possibly 20%).
   e. Expansion of central supply to support these services.
   f. Expansion of laboratory, radiology, pharmacy and other departments to support these services.
   g. Expansion of blood bank for increased bleeding operations. Up to 40% of casualties may require treatment for shock. If possible the blood bank activities should be located away from clinical services for casualties.
   h. Expansion of dietary services to provide food for casualties and personnel. Reorganization may include the provision of easily prepared nutritious meals, and additional hours for food service.
   j. Expansion of mortuary service. It is estimated that 10% of casualties may not survive the first 24 hours following admission.
7. Plans for the organization of clinical services:
   a. Triage is a very important factor in effective clinical organization. The role of the triage officer in the clinical services is a most important one. The decisions of the triage officer are of such magnitude that a highly competent staff member should be appointed to this position. He would be in charge of the receiving area and immediately examine all injured, determine the admission priority and designate the treatment area to which the casualty will be sent. It is important that the grave responsibility of the triage officer be recognized and his decisions regarding casualties be accepted by all concerned.
   b. Clinical organization should provide for a smooth transfer of casualties from triage area to hospital wards, operating rooms or recovery rooms.
   c. Physicians, dentists, nurses and veterinarians should be utilized without incurring any wastage of professional skills.
   d. Relocation or expansion of receiving area may be necessary to facilitate the rapid triage and transfer of casualties.
   e. Hospitals located near target areas should include

a casualty unit on hospital grounds so that casualties with minor injuries may be treated away from the main buildings of the hospital thus averting congestion.

8. The provision of an increase in inventories of supplies and equipment designed for essential lifesaving treatment of casualties to cover the first hours following a disaster until supplies can be made available from other sources.

9. The organization of an information unit adjacent to hospital grounds:
   a. This would be the only authorized channel through which all information should be given to relatives, the public and the press.
   b. Hospital identification and information index cards would be kept by this unit.
   c. Auxiliary police protection should be provided to assist in controlling traffic and personnel coming to the information unit and other units within the hospital grounds. In the interest of efficient operation of hospital services, only duly authorized persons should be allowed to enter hospital grounds.

10. The development of a personnel pool:
    a. The need for assistance by both professional personnel and auxiliary workers will be far in excess of that which can be provided by the present hospital staff. Reduction in routine and non-essential procedures and extension of hours of duty will be of considerable assistance. A large number of volunteers will be needed to meet hospital requirements. The personnel pool should include volunteers recruited from local and supporting areas.
    b. The personnel pool should be located in nearby vicinity.
    c. All distribution of personnel to supplement hospital staff should be made through this pool.
    d. Volunteers who are recruited prior to disaster should receive indoctrination and training in their assignments.

11. A plan designed to maintain a current disaster organization:
    a. All hospital personnel should be periodically oriented in the details of the hospital disaster plan i.e. at staff and other group conferences.
    b. Efficiency of the disaster organization can be enhanced by periodic maneuvers and drills involving all hospital personnel.

Hospitals taking cognizance of these elements in disaster preparedness will be provided with considerable protection against emergencies of either a major or minor nature regardless of cause.

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CORRESPONDENCE

FINANCING MEDICAL EDUCATION

To the Editor: Your editorial comments in the March 25 issue of the *Journal* regarding present-day costs of the medical student and accumulated debts on graduation prompt a comparison with the experiences of a preceding generation.

Before World War II such expenses were met by parents or relatives, by various and sometimes menial student jobs and frequently by loans at current interest rates ranging from 6 to 8 per cent. There was no G. I. or other governmental assistance. After various types of self-help I emerged from medical school in 1908 with what at that period seemed to represent a war debt — something in excess of $6,000 (exclusive of premedical and postgraduate training) entirely through advances or bank loans personally indorsed by a friend; this amount is more significant since this preceded the dollar devaluation of later years. Repayment was not easy, nor was it then deemed too difficult since the economic philosophy of that period had not come under the influence of government subsidy.

CLOUGH TURRILL BURNETT, M.D.
Denver, Colorado

BUSINESS VERSUS MEDICINE

To the Editor: Many doctors are concerned over the increasing use of the word "business" in association with our profession, holding that the practice of medicine is not a business and that the use of the word naturally heightens the critical attitude that the laity is presenting against the profession. It is the physician in business who has caused the present furor. To be sure, the word originates from "busy" or that which "busies one." And doctors do like to have butter on their bread. But we notice that to a layman the word "business" in any connection with a doctor has a bitter taste. With scientists, that is not true because scientists can ethically sell their knowledge and skills to the business market in ways unethical for doctors. Salesmen stating prices on refrigerators can say, "These are standard prices. Take them or leave them." What do we think of doctors who say such things? The dean of every school of medicine is expected to recognize the pith of this matter, and the dean tries to weed out before the start all candidates for admission whose attitudes suggest that they may be wishing to study medicine to make a business of it or who seek its knowledge and skills with the objectives of business gains. In business if a man is a cheat that is bad enough. But in medicine if a doctor or a surgeon is a cheat . . . what is it? Even the mental picture suggests such contrasts between business and medicine that some prefer never to speak the two words in the same breath. To gain financial reward is the objective of business. To advance the science and the art of medicine and to serve mankind are the objectives of the doctor. A science teaches us to know, and an art to do.

What word, then, should be used? "It were easier to tell twelve men what were best to be done than to be one of the twelve to follow mine own instruction." Someone may come up with the best word while we are trying to avoid the worst. No secret can be told to any who divined it not before. But I know no keener suggestion of the truth than that spoken fifty years ago by James Bryce before the dinner guests honoring General Gorgas: "Medicine is the only profession that labors incessantly to destroy the reason for its own existence."

SARAH PARKER WHITE, M.D.
Boston

NARCOTIC REGISTRATION

To the Editor: Physicians are reminded that, to comply with the provisions of the Harrison Narcotic Act, the application Form 678 must be executed and returned to the District Director of Internal Revenue at 174 Ipswich Street, Boston, on or before July 1 with remittance covering the tax.

When returns are not filed within the time prescribed by law, the penalties provided therein become applicable.

Persons who do not contemplate renewing their registration for the coming fiscal year should notify the District Director before July 1 with a view to surrendering any unused narcotic order blanks and arranging for disposal of any narcotics that they may have in their possession.

It is requested that this letter be inserted in the *New England Journal of Medicine* to remind physicians of their obligation to accomplish registration on time.

FRANK J. CAVANAGH
District Director
Internal Revenue Service
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Pediatric Gynecology: With sections on urology and proctology. By Goodrich C. Schauffler, M.D., assistant clinical professor of obstetrics and gynecology, University of Oregon Medical School. Third edition, 8°, cloth, 318 pp., with 76 illustrations. Chicago: Year Book Publishers, Incorporated, 1953. $7.50.

The author has completely revised this new edition of a book last published in 1947 to bring the text up to date. There is a new chapter on embryology. The book is well illustrated and well published.

Treatment of Toxic Goiter with Radioactive Iodine. By Lindon Seed, M.D., director, Isotope Laboratory, Grant Hospital, and clinical associate professor of surgery, University of Illinois College of Medicine; and Theodore Fields, M.S., assistant director, Radioisotope Laboratory, Hines Hospital, certified medical nuclear physicist, American Board of Radiology, and instructor in radiology, Northwestern University Medical School. Preface by George V. LeRoy, M.D., associate dean, Division of Biological Sciences, University of Chicago. 8°, paper, 116 pp., with 6 tables and 17 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 197, *American Lecture Series.)*

The authors have surveyed the literature on their subject with special reference to a simple and reliable test of thyroid function and the nonsurgical treatment of hyperthyroidism. There is a bibliography of 116 references and a good index. The monograph should be in all collections on the thyroid gland and on isotopes.

On the Nature of the Myocardial Contraction: A study of the electrolytes. By F. Lenzi and A. Caniggia. Preface by Professor Guido Izar. From the Clinic of Internal Medicine of the University, Siena (Italy). 8°, paper, 112 pp., with 19 illustrations. Basel: S. Karger, 1953. 14.55 Swiss francs.

This monograph discusses the two prominent theories of muscular contraction, the adenosinetriphosphoric acid and the electrolytic, with special reference to the electrolytes and myocardial contraction studied by the electrocardiogram. The literature has been reviewed, and there is an extensive bibliography. The small book should be in collections on cardiology and physiology.

Rudolf Virchow: Doctor, statesman, anthropologist. By Erwin H. Ackerknecht, M.D. 8°, cloth, 304 pp., with 2 illustrations and frontispiece. Madison: University of Wisconsin Press, 1953. $5.00.

Psychosomatic Research. By Roy R. Grinker, M.D., director of the Institute for Psychosomatic Research and Training, Michael Reese Hospital, Chicago, and clinical professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 207 pp. New York: W. W. Norton and Company, Incorporated, 1953. $3.50.

Heredity in Health and Mental Disorders: Principles of psychiatric genetics in the light of comparative twin studies. By Franz J. Kallmann, M.D., principal research scientist (medical genetics), New York State Psychiatric Institute, and assistant professor of psychiatry, Columbia University College of Physicians and Surgeons. With a foreword by Nolan D. C. Lewis, M.D. 8°, cloth, 315 pp., with 89 illustrations and 20 tables. New York: W. W. Norton and Company, Incorporated, 1953. $6.00.

Drives, Affects, Behavior. Edited by Rudolph M. Loewenstein, M.D. 8°, cloth, 399 pp. New York, New York: International Universities Press, Incorporated, 1953. $7.50.

Epilepsy and the Functional Anatomy of the Human Brain. By Wilder Penfield, O.M., C.M.G., M.D. (Johns Hopkins), B. Litt. and D.Sc. (Princeton), B.Sc., and D.Sc. (Oxon.), F.R.C.S., F.R.S.; and Herbert Jasper, M.D., C.M. (McGill). 8°, cloth, 896 pp., with 314 illustrations and 8 color plates. Boston: Little, Brown and Company, 1954. $16.00.

NOTICES

SOUTH END MEDICAL CLUB

The June meeting and the annual outing of the South End Medical Club will be held at Prendergast Preventorium of the Boston Tuberculosis Association, 1000 Harvard Street, Mattapan, on June 22 at 12 noon. Dr. Eli Friedman, associate professor of pediatrics, Boston University School of Medicine, will speak on the subject "The Treatment of Tuberculosis Meningitis." All physicians are invited.

SOCIETY MEETINGS AND CONFERENCES

June 14–16. American Neurological Association. Page 540, issue of March 25.

June 15–18. Medical Library Association. Page 491, issue of March 18.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.

June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.

June 22. South End Medical Club. Notice above.

June 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

August 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

August 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 13–15. American Association of Blood Banks. Page 968, issue of June 3.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

September 22. New England Pediatric Society. Page 968, issue of June 3.

October 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

October 31-November 4. American Institute of Dental Medicine. Page 968, issue of June 3.

November 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

December 8. New England Pediatric Society. Page 968, issue of June 3.

December 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 340, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 17

THURSDAY, JUNE 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Thoracic Conference. Diaphragmatic Hernia. Dr. William Oren. Main Amphitheater, Peter Bent Brigham Hospital.

(Notices concluded on page xxxiii)